



Achieving Equilibrium: An Examination of the FDA's Attempt to Balance Patient Safety with Access to Innovative Treatments Through the Off-Label Marketing Regulations

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**ACHIEVING EQUILIBRIUM: AN EXAMINATION OF THE FDA'S
ATTEMPT TO BALANCE PATIENT SAFETY WITH ACCESS TO
INNOVATIVE TREATMENTS THROUGH THE OFF-LABEL
MARKETING REGULATIONS**

by,

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ABSTRACT

The FDA maintains almost complete control over the approval, labeling, and marketing of prescription drugs. Pharmaceutical companies are generally prohibited from promoting their products to doctors for any use other than the ones that have been explicitly approved by the FDA. However, doctors may prescribe drugs that have been approved by the FDA to their patients for any purpose for which they believe it will be beneficial. In 1997, Congress passed the Food and Drug Modernization Act (FDAMA) which created a limited exception that allows drug manufacturers who submit a supplemental new drug application to the FDA for a new use of an approved drug to send limited materials directly to doctors. In enacting the provisions, Congress sought to balance the competing interests of patient access to innovative treatments with consumer protection and patient safety.

However, these provisions and the regulations the FDA promulgated under them have drawn significant criticism. Certain critics contend that the restrictions on off-label marketing stifle innovation and keep beneficial treatments from patients who need them. Others argue that these exceptions expose patients to significant risk by encouraging them to take drugs that have not been proven safe and effective under the FDA standards. This paper argues that the regulatory scheme developed under the FDAMA represents a proper balance between patient safety and access to innovative drugs because it seeks to facilitate the education of doctors rather than the promotion of drugs. However, the FDA can go further under the current regulatory scheme to find affordable ways to get reliable information to doctors, while still protecting patient safety. By focusing on finding new means to provide doctors with reliable, unbiased information the FDA can do just that.

INTRODUCTION

Americans rely heavily on drugs to cure what ails them, improve their mood and health, and generally make them feel better. We can go to our local drug stores to pick up over the counter remedies for our headaches or colds. However, modern medicine also relies heavily on the use of prescription drugs that we must get from our doctors. While doctors have very few legislative or regulatory restrictions on their ability to prescribe drugs to patients, the drug manufacturers who create, produce, and market the drugs to doctors do. The Food and Drug Administration (FDA) is authorized by Congress to protect the public health by promoting the safety and efficacy of prescription drugs sold on the U.S. market.¹ Specifically, the FDA's mission is:

“(1) To promote and protect the public health by helping safe and effective products reach the market in a timely way,
(2) To monitor products for continued safety after they are in use, and
(3) To help the public get the accurate, science-based information needed to improve health.”²

To this end, the FDA is authorized to create product standards, regulate the marketing of drugs to consumers and physicians, control which drugs enter the US market, and provide information to the public.³ In short, the FDA retains almost complete power over the production, creation, and promotion of prescription drugs.

The underlying assumption is that the public needs protection from the profit-driven pharmaceutical industry that would endanger it by putting under-researched or ineffective drugs on the market. To this end, the FDA prohibits drug manufacturers from marketing their drugs “off-label,” or for any use for other than the use it was approved for. However, while it limits

¹ 21 U.S.C.A. §393(b)(1) (2008).

² FDA Overview: Protecting Consumers Promoting Public Health, <http://www.fda.gov/oc/opacom/fda101/sld001.html> (last visited Apr. 19, 2008).

³ *Id.*

the access of drug manufacturers to public markets, the FDA also seeks to promote public access to safe and effective drugs. And, while the FDA maintains considerable power over the pharmaceutical industry, it does not regulate doctors or medical practices. Doctors then have the discretion to prescribe any drug on the market for any uses, those that have been officially accepted by the FDA and those that have not.

In the past two decades, the FDA has begun to permit manufacturers to disseminate limited information to physicians about the off-label uses of drugs. These exceptions to the off-label marketing prohibition intend to promote pharmaceutical research about new uses of approved drugs and get reliable information to physicians about potentially beneficial treatment options in a timely manner. However, these provisions have drawn criticism from all sides. On the one hand, critics argue that they reduce patient safety by exposing more patients to drugs that have not been tested for safety and efficiency. On the other hand, critics argue that these provisions do not go far enough to encourage innovation and facilitate getting new treatments to the patients who need them. This paper will examine both sides of the off-label marketing debate to analyze whether the current regulatory scheme strikes a proper balance between patient safety and access to innovative treatments.

Section I defines the concept of “off-label marketing.” Section II then reviews the historical development of the FDA’s regulatory authority over drug development, approval, labeling, and promotion. Section III summarizes the Food and Drug Modernization Act of 1997 and the regulatory framework for off-label marketing under which we operate today. Section IV outlines the popular arguments put forth in the literature. Section V describes some popular suggestions put forth by academics and practitioners about how to improve the system. And

Section VI suggests a new way to consider the issue and proposes a solution that could both promote patient safety and facilitate innovation at the same time.

I. OFF-LABEL MARKETING DEFINED

Under the Federal Food, Drug, and Cosmetic Act, pharmaceutical manufacturers may not promote a drug for any use other than the one for which it obtained FDA approval.⁴ Drug labels then the use for which the FDA has approved the drug.⁵ This paper borrows its definition of off-label use from William Christopher's article, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*.⁶ Off-Label use of a drug includes "using an approved drug to treat a disease that it not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use."⁷

Off-label marketing then occurs when a drug manufacturer promotes their drug for an off-label use. This paper's definition of marketing reflects the FDA's broad definition of promotion which includes: "advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."⁸ Promotional materials also include any communication or material which in any way describes the drug issued by or on behalf of the manufacturer, packer, or distributor of the drug.⁹ While all drugs can be used and marketed off-label (though not

⁴ Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301). *See infra* Section V.C.1. (outlining the drug approval and labeling requirements).

⁵ 21 C.F.R. § 201.128 (2008).

⁶ William Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993).

⁷ *Id.*

⁸ 21 C.F.R. § 202.1(l)(1) (2008).

⁹ *Id.* § 202.1(l)(2).

necessarily legally), this paper discusses only prescription drugs, which patients must get through a physicians rather than over the counter drugs which patients can buy directly from a retail outlet.

II. HISTORY OF THE REGULATION OF PRESCRIPTION DRUGS

A. THE FEDERAL FOOD AND DRUGS ACT: A NATIONWIDE SYSTEM FOR REGULATING HUMAN DRUGS

The 1906 Food and Drugs Act¹⁰ created a nationwide regulatory system for all human drugs.¹¹ The 1906 Act prohibited the distribution in interstate commerce of any food and drugs that were adulterated or misbranded. Congress gave the FDA the power to take misbranded drugs off the market through a court order.¹² It also provided criminal sanctions for introducing misbranded drugs into the marketplace.¹³ However, under the Act, the FDA had no pre-market authority to seize drugs or to demand proof that the drug was safe or effective.¹⁴

Under the statute a drug was “misbranded” if it made “false or misleading statements regarding a food or drug on the package or label thereof.”¹⁵ The 1906 Act also prohibited the sale of imitation drugs or fakes. The only labeling requirements for drugs under the statute were that any ingredients listed on the packaging must be factually true, drug imitations had to be

¹⁰ Food & Drugs Act, Ch. 3915, 34 Stat. 768 (1907).

¹¹ Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1754, 1758 (1996). Congress had regulated biological drugs four years earlier in the Biologics Act of 1902, 32 Stat. 728. The law was passed as a response to the selling of a diphtheria vaccine that was infected with tetanus and which had killed several children in 1901. PETER BARTON HUTT & RICHARD A. MERRILL, *FOOD AND DRUG LAW: CASES AND MATERIALS* 8-9 (2d ed. 1991). That act required pre-market approval for biological products such as vaccines for safety and efficacy. *See id.*; Merrill, *supra*, at 1758.

¹² Food & Drugs Act, §10, 34. Stat. at 771.

¹³ *Id.* § 2 at 768.

¹⁴ *See* Merrill, *supra* note 11, at 1758.

¹⁵ Lauffer Hayes & Frank Ruff, *The Administration of the Federal Food and Drugs Act*, 1 L. & CONTEM. PROBLEMS 16 (1933), *reprinted in* HUFF & MERRILL, *supra* note 11, at 9.

clearly labeled as such, and drug labels had to state the quantity of any narcotics which were present in the drug.¹⁶

The 1906 Act's definition of misbranding did not prohibit false efficiency or therapeutic claims, although the FDA tried to argue that it did in *United States v. Johnson*.¹⁷ In that case, the government indicted a drug manufacturer for misbranding under the Act for shipping drugs between states which it falsely claimed cured cancer. The Supreme Court held that the statute did not prohibit all false claims, but rather only prohibited false claims that "determine the identity of the article."¹⁸ Congress responded to the court's holding in *Johnson* by amending the 1906 Act so that the definition of misbranded included any statement on the labeling which was false or fraudulent.¹⁹ However, the fraudulence requirement of the Act meant that the government had to prove that the seller knew that the statements on the packaging were false.²⁰

Because it was unable to prevent the drug from entering the market place in the first place and was only able to remove the drug if it could prove that the seller intended to commit fraud, the FDA's ability to prevent misbranded drugs from being sold was extremely limited under the 1906 Act.²¹ It remained so for several decades until a tragedy in 1937 spurred Congress into action.

¹⁶ Food & Drugs Act, §8, 34 Stat. at 770-71. *See also id.* at 10.

¹⁷ 221 U.S. 488, 489-90 (1911).

¹⁸ *Id.* at 497; *see* Merrill, *supra* note 11, at 1759.

¹⁹ Ch. 352, 37 Stat. 416, §8 at 417 (1912). *See also* Merrill, *supra* note 11, at 1759; Katherine A. Helm, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 125 (Autumn 2007).

²⁰ Merrill, *supra* note 11, at 1759.

²¹ *Id.* *See also* Helm, *supra* note 19, at 125-26.

During September and October of 1937, a drug, Elixir Sulfanilamide, killed more than 100 people, many of them children, in over 15 states.²² Sulfanilamide had been sold in tablet and powder form to cure streptococcal infections.²³ However, in 1937, the company that manufactured it produced a liquid version of the drug, which included diethylene glycol, a highly poisonous ingredient normally used as antifreeze. The company tested for flavor, appearance, and fragrance, but not for safety, and then sent the elixir all over the country.²⁴ By the time the FDA was notified of the deaths and initiated the first nationwide recall of a drug, 633 shipments of the elixir had been sent all around the country and 105 people had been killed.²⁵ This incident would likely have been prevented had the FDA had the authority to require pre-market safety testing. Congress created a system for pre-market FDA notification of drugs in the 1938 Food, Drug, and Cosmetic Act.²⁶ This system became the beginning of our current system of pre-market approval.²⁷

B. FEDERAL FOOD, DRUG, AND COSMETIC ACT: PRE-MARKET NOTIFICATION

The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) required drug manufacturers to test drugs for safety and provide the results of the tests to the FDA before introducing the drugs to the market.²⁸ The most significant innovation of the FDCA was the creation of the

²² Carol Ballentine, *Taste of Raspberries, Taste of Death: the 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAG., June 1981, available at <http://www.fda.gov/oc/history/elixir.html>.

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ Food, Drug & Cosmetic Act, Ch. 675, 52 Stat. 1040 (1938) (current version at 21 U.S.C. §§ 301-99 (2007)) [hereinafter FDCA].

²⁷ See Merrill, *supra* note 11, at 1762.

²⁸ FDCA § 505(a)-(c), 52 Stat. at 1052 (1938). Merrill, *supra* note 11, at 1761-62; Helm, *supra* note 19, at 127.

“new drug” category of drugs.²⁹ The FDCA defined a “new drug” as: “any drug the composition of which is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”³⁰ Before a drug manufacturer could market a new drug, it had to submit an effective New Drug Application (NDA) to the FDA. The New Drug Application had to provide the results of safety trials, detail the chemical makeup of the drug, and describe how the drug would be manufactured.³¹ A NDA automatically became effective 60 days after it was submitted to the FDA unless the FDA either disapproved it or notified the applicant that it was extending its review to 180 days.³²

The FDCA also gave the FDA the authority to control many aspects of drug labeling. Under the new statute, a drug was mislabeled if its labeling was “false or misleading in any particular.”³³ Thus, the government no longer had to prove that the seller committed intentional fraud to remove a drug from the market for false labeling. Moreover, the FDCA required that the drug be labeled with considerable safety and dosage warnings and “adequate directions for use.”³⁴ And, drug manufacturers had to get approval from the FDA if they sought to change their product’s labeling.³⁵

While the FDCA significantly expanded the power of the FDA to regulate the pre-market approval of drugs, this power was still considerably limited. First, under the FDCA, the FDA

²⁹ FDCA § 201(p), 52 Stat. at 1041-42 (1938). Merrill, *supra* note 11, at 1761; Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEORGETOWN L.J. 185 (1971), reprinted in HUTT & MERRILL, *supra* note 11, at 476.

³⁰ FDCA § 201(p)(1), 52 Stat. at 1041-42 (1938).

³¹ *Id.* § 505(b), 52 Stat. at 1052.

³² *Id.* § 505(c), 52 Stat. at 1052.

³³ *Id.* § 502(a), 52 Stat. at 1050.

³⁴ *Id.* § 502(f)(1)-(2), 52 Stat. at 1051.

³⁵ *Id.* § 502(g), 52 Stat. at 1051.

was only permitted to evaluate the safety of drugs before they could be marketed to the public; it did not give the FDA the power to evaluate the efficacy of new drugs.³⁶ Second, the Act did not extend to the FDA the power to evaluate the safety of all drugs before they went to market. The FDCA only applied to drugs that were not already on the market.³⁷ The FDCA left the drug manufacturers with the discretion to decide if the drug they were introducing to the market was generally recognized as safe, and therefore, not “new.” “Consequently, a manufacturer could introduce a drug whose safety FDA had no opportunity to review.”³⁸

The 1938 Act also left to drug manufacturers the ability to categorize their drug as prescription or non-prescription.³⁹ However, in 1951, Congress passed the Durham-Humphrey Amendment which, for the first time distinguished between those drugs that could be marketed and sold directly to consumers and those that had to be dispensed only through licensed physicians.⁴⁰ Those drugs that could not be labeled with directions sufficient to make them safe for unsupervised use or those that were too toxic for unsupervised use were deemed prescription drugs. Those that did not present these risks and challenges were deemed non-prescription, or over-the-counter (“OTC”), drugs.⁴¹ The FDCA and Durham-Humphrey Amendment “architected the FDA’s role as guardian of public safety in the drug industry.”⁴² However,

³⁶ See Merrill, *supra* note 11, at 1762; Note, *Drug Efficacy and the 1962 Drug Amendments*, *supra* note 29, at 477.

³⁷ FDCA § 210(p)(1), 52 Stat. at 1042 (1938).

³⁸ Merrill, *supra* note 11, at 1762. See JERRY MASHAW & RICHARD A. MERRILL, *THE AMERICAN PUBLIC LAW SYSTEM* 463, 498 (1st ed. 1975); HUTT & MERRILL, *supra* note 11, at 478.

³⁹ Helm, *supra* note 19, at 127.

⁴⁰ Durham-Humphrey Amendment, ch. 578, 65 Stat. 648 (1951) (codified as amended at 21 U.S.C. § 353) (2008).

⁴¹ *Id.* 65 Stat. at 648-49 (codified as amended at 21 U.S.C. § 353(b)(1)(A)) (2008).

⁴² Helm, *supra* note 19, at 128.

without being able to assess the medical benefits of a drug, staff at the FDA understood that they could never truly evaluate whether a drug was safe.⁴³

C. THE 1962 DRUG EFFICACY AMENDMENTS: EFFECTIVENESS AND SAFETY

Congress finally gave the FDA the power to evaluate the efficacy of new drugs in the 1962 Kefauver-Harris Amendments, which prohibited the shipment of any new drug in interstate commerce without FDA approval of its safety and efficacy.⁴⁴ In addition to creating an efficacy requirement, the Kefauver-Harris Amendments made two other significant changes to the drug review process.⁴⁵ First, they transformed the FDCA's pre-market notification system, in which drug manufacturers could automatically proceed to market with a new drug if the FDA had not objected within 60 days, to a pre-market approval system in which they had to wait for explicit approval from the FDA to bring a new drug to market.⁴⁶ Second, they expanded the FDA's authority to oversee the design and implementation of the clinical trials that drug manufacturers employed to test the safety and efficacy of new drugs.⁴⁷ With the passage of the Kefauver-Harris Amendments, also known as the Drug Efficacy Amendments, Congress created the basic drug regulatory structure under which we operate today.⁴⁸

⁴³ Merrill, *supra* note 11, at 1764.

⁴⁴ Kefauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. §§ 321, 331-32, 348, 351-53, 357-60, 372, 374, 376, 381 (1970)) [hereinafter Kefauver-Harris Amendments]. *See also Note, Drug Efficacy and the 1962 Drug Amendments*, *supra* note 29, at 477; HUTT & MERRILL, *supra* note 11, at 477.

⁴⁵ Merrill, *supra* note 11, at 1764.

⁴⁶ *Id.* at 1765; *See also Note, Drug Efficacy and the 1962 Drug Amendments*, *supra* note 29, at 477.

⁴⁷ *Id.* at 1765-66; Helm, *supra* note 19, at 130.

⁴⁸ *See* Merrill, *supra* note 11, at 1764; Helm, *supra* note 19, at 129.

The efficacy requirement was added under the definition of new drugs, which Congress expanded to cover any drug that is not generally recognized as safe and effective.⁴⁹ The testing and reporting requirements for New Drug Applications were dramatically expanded as a result of the new efficacy requirement. In addition to showing that a new drug was safe, the drug manufacturer had to provide data demonstrating that the drug was effective for the therapeutic use for which it was being marketed.⁵⁰ Under the old system, once a drug manufacturer had shown that a drug was safe, it could have conceivably marketed it to the public for any number of therapeutic uses. However, the new definition of “new drug” in the Drug Efficacy Amendments meant that each use of a drug could require additional testing and FDA review.⁵¹ Unlike the 1938 Amendments, which exempted drugs already on the market from having to provide data on safety, the 1962 Amendments required the FDA to review all of the drugs that had been the subject of effective NDAs since the FDCA went into effect.⁵²

The Amendments required the FDA affirmatively to approve drugs for safety and efficiency before they could be marketed.⁵³ As Richard Merrill points out, “the law thus gave the FDA an effective veto over the marketing of any drug over about which it had reservations.”⁵⁴ Further, the Drug Efficacy Amendments extended the time that the FDA had to review the NDA from 60 days to 180 days.⁵⁵ If the FDA failed to make a decision in that time

⁴⁹ Kefauver-Harris Amendments, § 102(a)(2), 76 Stat. at 781.

⁵⁰ *Note, Drug Efficacy and the 1962 Drug Amendments*, *supra* note 29, at 477; Merrill, *supra* note 11, at 1765-66; Helm, *supra* note 19, at 129; HUTT & MERRILL, *supra* note 11, at 513.

⁵¹ Merrill, *supra* note 11, at 1765-66.

⁵² HUTT & MERRILL, *supra* note 11, at 478. The FDA had some trouble meeting this requirement it marked a large expansion of the FDA's power to regulate drugs on the market. For a full discussion of the FDA's efforts to evaluate the NDAs of drugs on the market for efficiency, see *id.* at 478-84.

⁵³ Kefauver-Harris Amendments, § 505(c)(1), 76 Stat. at 781.

⁵⁴ Merrill, *supra* note 11, at 1765.

⁵⁵ Kefauver-Harris Amendments, § 505(c), 76 Stat. at 781.

period, then the manufacturer could request a decision. However, few applicants ever pushed for a decision and only three times have rejected applicants challenged the FDA's decision in court.⁵⁶ Thus, the 1962 Amendments put drug manufacturers at the mercy of the FDA's efficiency, capacity, and priority to get their drugs to market.

Finally, the Drug Efficacy Amendments gave the FDA considerable authority over the design and implementation of the clinical trials that drug manufacturers used to test whether their products were safe and effective.⁵⁷ In addition to requiring that the FDA refuse approval for any drug about which it had lingering safety concerns, Section 505(d) was amended to require the FDA to reject any New Drug Application for which there was "a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof."⁵⁸ Moreover, under the new Section 505(e) under the Amendment, the FDA had to withdraw approval for any drug if it found "on the basis of new information before him with respect to such drug, evaluated together with the evidence available to [it] when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."⁵⁹ The Act defined "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and

⁵⁶ HUTT & MERRILL, *supra* note 11, at 532; Merrill, *supra* note 11, at 1766 n. 42. Applicants likely have not been inclined to push the FDA to move more quickly since to do so would be to agitate the entity controlling whether or not their product makes it to market.

⁵⁷ Kefauver-Harris Amendments, § 505(d), 76 Stat. at 781. *See also* HUTT & MERRILL, *supra* note 11, at 480; Merrill, *supra* note 11, at 1766; *Note, Drug Efficacy and the 1962 Drug Amendments*, *supra* note 29, at 477.

⁵⁸ Kefauver-Harris Amendments, § 505(d)(5), 76 Stat. at 781

⁵⁹ *Id.* § 505(e)(3), 76 Stat. at 782.

experience to evaluate the effectiveness of the drug involved.”⁶⁰ Because it was up to the FDA to determine what constituted substantial evidence, it had considerable control in shaping what kinds of clinical trials drug manufacturers could use to prove that their drugs did what they claimed to do.

Furthermore, before drug manufacturers could begin clinical trials on human beings, under the 1962 Amendments, they were required to submit an Investigational New Drug Application (INDA) to get FDA authorization to proceed with human clinical trials.⁶¹ The INDA had to include reports of preclinical testing “adequate to justify clinical testing”⁶² and had to detail the proposed clinical testing plan.⁶³ The Amendments thus gave to the FDA control over the preclinical research and the clinical trials that drug manufacturers employed to get a drug to the marketplace. “At the end of the day, drug makers must persuade FDA reviewers that they have submitted enough evidence to prove that a drug works. As a result, the agency has become the most influential source of guidance on the design of clinical drug studies in the country”⁶⁴

1. New Drug Application Process Under the Drug Efficacy Amendments

The 1962 Amendments granted to the FDA plenary control over the design, production, distribution, and marketing of new drugs to the marketplace. In order to exercise this new authority, the FDA set in place a series of regulations and guidelines outlining the requirements for approval of a New Drug Application.⁶⁵ The two aspects of the New Drug Approval

⁶⁰ *Id.* § 505 (d)(6), 76 Stat. at 781.

⁶¹ *Id.* § 505(i), 76 Stat. at 783, 21 U.S.C. §355(i) (amended 2004).

⁶² *Id.* § 505(i)(1), 76 Stat. at 783, 21 U.S.C. §355(i) (amended 2004).

⁶³ *Id.* § 505(i)(2)-(3), 76 Stat. at 783, 21 U.S.C. §355(i) (amended 2004).

⁶⁴ Merrill, *supra* note 11, at 1767. *See also* Helm, *supra* note 19, at 130.

⁶⁵ The history of these regulatory guidelines and is complex and out of the scope of this paper. For a detailed version of this history, see HUTT & MERRILL, *supra* note 11, at 477-510; Merrill,

application which were most significant to off-label marketing are the efficacy and labeling requirements.⁶⁶

a. Efficacy Requirements

“[The efficacy requirement] has . . . provided a solid basis for what the FDA describes as a solid regulatory regime in which pharmaceutical products cannot be promoted or suggested for any use in the absence of labeling for that approved use by the FDA.”⁶⁷ The Drug Efficacy Amendments sought to balance the risk of bringing unsafe or therapeutically ineffective drugs to market with the cost of delaying safe and effective drugs to market. The FDA was thus charged with developing a system for drug approval that would get safe and effective drugs to market as quickly as possible while preventing dangerous or ineffective drugs from being sold to U.S. consumers. To meet this end, the FDA developed a four-step process drug manufacturers must follow to get a new drug application approved.

First, drug manufacturers must conduct preclinical trials testing on animals. These trials must provide the manufacturer with data on the pharmacology and toxicity of the drug. The exact information the manufacturer is required to submit depends on the nature of the drug being tested. However, the pre-clinical investigations must supply the manufacturer with sufficient data on the pharmacological activity of the drug, such as how the drug is absorbed, distributed, metabolized, and excreted.⁶⁸ The investigations must also provide data on the acute toxicology

supra note 11, at 1768-1808. See generally David L. Stepp, *The History of FDA Regulation of Bio-Technology in the Twentieth Century*, 46 Food & Drug L.J. 1 (1999); Helm, *supra* note 19.

⁶⁶ Elizabeth A. Weeks, *Is it Worth the Trouble? The New Policy on Dissemination on Off-Label Drug Use Under the Food and Drug Modernization Act of 1997*, 54 FOOD & DRUG L.J. 645, 654 (1999).

⁶⁷ Thomas A. Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD & DRUG L.J. 57, 62 (1996). See also Merrill, *supra* note 11, at 1765-66; Weeks, *supra* note 66, at 654.

⁶⁸ 21 C.F.R. § 312.23(a)(8)(i) (2008).

of the drug in animals as well as generalized data to support that it is safe to proceed with clinical trials on humans.⁶⁹ The applicant must submit the data from these preclinical trials in the IND, as well as a description of the substance of the drug, a copy of the labeling that will be sent to the drug investigators, information on the laboratory practices of the applicant, and any information on previous human experience with the drug.⁷⁰ The drug sponsor must also submit a detailed protocol plan for how it will conduct the clinical trials. If the FDA approves and a local Institutional Review Board approves the IND, then the drug sponsor may move ahead to clinical trials in humans.⁷¹

The human trials consist of three phases and require informed consent from the subjects of the studies.⁷² In Phase I, investigators seek to determine the safety of the drug for use in human subjects and generally do not create data on efficacy.⁷³ Specifically these studies, which are typically done on a small number of healthy subjects (between 20 and 80 normally⁷⁴), seek to determine the toxicity of the drug, how it's metabolized and excreted, and also look for adverse effects.⁷⁵ To this end, the investigator will administer the drug at very low dosages in the beginning and then increase the dosage very gradually if the drug does not show harmful effects at the lower dosages. If there are significant adverse effects, the drug manufacturer will abandon

⁶⁹ *Id.* § 312.23(a)(8)(ii)(a)-(b) (2008).

⁷⁰ *Id.* § 312.23(a)(3)-(4), (7)-(9) (2008).

⁷¹ *Id.* § 312.22(a) (2008). *See also* Helm, *supra* note 19, at 129-30; Weeks, *supra* note 66, at 654-55; HUTT & MERRILL, *supra* note 11, at 515.

⁷² 21 C.F.R. § 312.21 (2008); HUTT & MERRILL, *supra* note 11, at 517; Weeks, *supra* note 66, at 655.

⁷³ THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS, REPORT OF THE SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY OF THE HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY, 96th Cong., 2d Sess. (1980), *reprinted in* HUTT & MERRILL, *supra* note 11, at 516; Weeks, *supra* note 66, at 655.

⁷⁴ 21 C.F.R. § 312.21(a)(1)

⁷⁵ *Id.* § 312.21(a)(1)-(2) (2008); THE FOOD AND DRUG ADMINISTRATION'S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516; Weeks, *supra* note 66, at 655; Helm, *supra* note 19, at 129.

the trials and the drug at Phase I.⁷⁶

Phase II is the initial stage at which the drug is tested on people who have the condition or disease the drug is designed to treat to gather initial data on efficacy, dosage at which the drug is effective, side effects, and risks.⁷⁷ Phase II also involves a small number of subjects, usually no more than a few hundred.⁷⁸ As in Phase I, the protocols will usually begin by giving subjects low dosages and then increasing the dosages as the trials continue.⁷⁹ If the drug does not prove to be effective at this phase, then it will be abandoned. If the drug is safe and effective in these small trials, then the study will proceed to large-scale clinical trials in Phase III.⁸⁰

Phase III trials are to evaluate the benefits and risks of the drug as a whole as well as to “provide a basis”⁸¹ for labeling.⁸² They are usually double-blind experiments in which a control group receives a placebo and can involve thousands of patients.⁸³ Investigators in Phase III trials will pay particular attention to side effects, adverse reactions, and negative interactions with other medications.⁸⁴ If the drug manufacturer can complete two Phase III trials which demonstrate efficacy without significant adverse reactions and which are scientifically sound, the data for these two studies will then be submitted for approval to the FDA as part of the New

⁷⁶ THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516.

⁷⁷ 21 C.F.R. § 312.21(b). *See also id.*, THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516; Weeks, *supra* note 66, at 655; Helm, *supra* note 19, at 129.

⁷⁸ 21 C.F.R. § 312.21(b).

⁷⁹ *Id.* *See also* THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516.

⁸⁰ THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516; Weeks, *supra* note 66, at 655; Helm, *supra* note 19, at 129.

⁸¹ 21 C.F.R. § 312.21 (c)

⁸² *Id.*

⁸³ *Id.* *See also* THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516; Weeks, *supra* note 66, at 655; Helm, *supra* note 19, at 129

⁸⁴ THE FOOD AND DRUG ADMINISTRATION’S PROCESS FOR APPROVING NEW DRUGS, *supra* note 73, at 516.

Drug Application.⁸⁵ Only one of ten drugs for which a sponsor obtained an IND, will have enough promising data to submit an NDA.⁸⁶

The FDA requires drug manufacturers to present new and substantial evidence to support every therapeutic indication for a particular drug.⁸⁷ This rule applies to pre-market drugs and drugs for which a manufacturer has already gotten approval for one use. When a manufacturer wishes to market a drug for a use other than the one for which it has FDA approval, it must file a Supplemental New Drug Application (SNDA) to gain approval for the new use.⁸⁸ In addition to a new therapeutic use for a drug, manufacturers must file a SNDA for any new aspects of a drug which require a change to the drug's labeling, including change in dosages, strength of the drug, changes in ingredients or design of the drug, change in populations the drug is used to treat, or manufacturing changes.⁸⁹ The SNDA must contain new data from new clinical trials that demonstrate the drug's effectiveness for the unapproved use.⁹⁰ Under the FDA Guidelines, manufacturers are generally permitted to submit the preclinical data and the data from the original Phase I clinical trials in support of the new use application.⁹¹ However, the sponsor of the application must conduct new Phase II and Phase III studies to show that the drug is effective for the new indication.⁹²

Phase III clinical trials are the most expensive and time consuming part of the drug

⁸⁵ *Id.*

⁸⁶ *Id.*; Weeks, *supra* note 66, at 655.

⁸⁷ Merrill, *supra* note 11, at 1853 n. 316; Weeks, *supra* note 66, at 655.

⁸⁸ *Id.* Helm, *supra* note 19, at 130.

⁸⁹ FDA Drug Approvals List, Notes on Effectiveness Supplemental Code Definitions, <http://www.fda.gov/cder/da/da.htm> (last visited on Apr. 22, 2008).

⁹⁰ *Id.*

⁹¹ Merrill, *supra* note 11, at 1853 n. 316; Weeks, *supra* note 66, at 655.

⁹² *Id.*

approval process.⁹³ And, once a drug is approved for one use, drug manufacturers “face strong disincentives against seeking permission to market off-label uses of their products.”⁹⁴ This pressure is further exacerbated by the fact that once the original drug is approved for the new use, patents barring generic drug imitations of the original drug might have expired and the generic drug will also be approved for the new use; thus reducing the manufacturers projected revenue from the new use.⁹⁵

Though drug manufacturers are prohibited from marketing a drug for uses for which they are not approved, physicians are permitted to prescribe drugs for uses other than their approved indications.⁹⁶

“If an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of Section 505 of the Act are satisfied. Once the new drug is in a local pharmacy, . . . , the physician may, as part of the practice of medicine lawfully prescribe a different dosage for his patient or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the FDA.”⁹⁷

While “off-label” uses of prescription drugs are commonplace in medical practice, any promotion by manufacturers of indications that the FDA has not approved are a violation of the FDCA.⁹⁸ The FDA defines promotion broadly, “stated simply, its view is that any material describing uses of the drug that is distributed by or at the direction of the manufacturer –

⁹³ Id.

⁹⁴ Weeks, *supra* note 66, at 655-66.

⁹⁵ Helm, *supra* note 19, at 165.

⁹⁶ Merrill, *supra* note 5, at 1853 & n. 317-18; Helm, *supra* note 19, at 130; Weeks, *supra* note 66, at 647; HUTT & MERRILL, *supra* note 11, at 618-22; *Use of Unapproved Drugs for Unlabeled Indications*, 12 FDA DRUG BULL., Apr. 1982, at 5.

⁹⁷ *Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rule Making*, 37 FED. REG. 16,503 (1972), reprinted in HUTT & MERRILL, *supra* note 11 at 619-22.

⁹⁸ Merrill, *supra* note 5, at 1855; HUTT & MERRILL, *supra* note 11 at 618-31; Kaspar J. Stoffelmayr, *Comment, Products Liability and “Off-Label” Uses of Prescription Drugs*, 63 U. CHI. L. REV. 275, 279-81 (1996).

regardless of whether the material was authored by the manufacturer—constitutes “promotion.”⁹⁹

This paper will discuss the FDA regulations on off-label promotion in greater detail in Section III.

b. Labeling Requirements

Section 201 of the FDCA defines labeling as: “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”¹⁰⁰ The FDA advocated a broad definition of labeling in *Kordel v. United States*¹⁰¹ in 1948. In that case, the Supreme Court agreed with the FDA that “accompanying such article” included materials that were not physically attached to the drug or even shipped with the drug. Rather, than the physical proximity, the court said, “it is the textual relationship that is significant.”¹⁰² If the materials contain information about the drug that is descriptive or instructive, then they count as labeling. A drug label for a prescription drug “must provide ‘full disclosure,’ which means adequate information concerning its safety and effectiveness for its intended use by the practitioner who dispenses it. Each prescription drug package must include information that fully discloses any warnings and provides adequate directions for proper use.”¹⁰³

The 1938 FDCA gave the FDA the power to regulate the labeling of prescription drugs.¹⁰⁴ However, the FDA enforced labeling requirements primarily through the misbranding provisions of the FDCA.¹⁰⁵ It did not have the authority to review claims of effectiveness on the

⁹⁹ Merrill, *supra* note 5, at 1855.

¹⁰⁰ FDCA § 201(m) (1938) (codified as amended at 21 U.S.C. §321(m) (2008)).

¹⁰¹ 335 U.S. 345 (1948).

¹⁰² *Id.* at 350.

¹⁰³ Hayes, *supra* note 67, at 61.

¹⁰⁴ Weeks, *supra* note 66, at 656; 21 U.S.C. §321(k).

¹⁰⁵ Merrill, *supra* note 5, at 1758-61; Weeks, *supra* note 66, at 656; Hayes, *supra* note 67, at 61.

drug and could only remove a drug after it had been placed on the market if the labeling was “false.”¹⁰⁶ With the passage of the Drug Efficacy Amendments, the FDA was granted the authority to control labeling through the new drug approval process. Now, the drug sponsor must submit its proposed labeling with the NDA¹⁰⁷ and the FDA can deny approval if the manufacturer fails to submit labeling or if the FDA finds that the labeling proposed is inadequate for the drugs intended use.¹⁰⁸

The FDA first promulgated a regulation defining intended use in 1951, after the Ninth Circuit, in *Alberty Food Products v. United States*¹⁰⁹ held a product misbranded when its labeling did not state a therapeutic use that was advertised in a newspaper advertisement. The “intended use” of a drug “refers to the objective intent of the persons legally responsible for the labeling of drugs.”¹¹⁰ Intent may be shown in a number of ways including the labeling of the products, claims in advertisements, public statements, and the general circumstances surrounding the product.¹¹¹ The regulations state that:

“If a manufacturer knows, . . . , that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.”¹¹²

The drug manufacturer’s responsibility to provide labeling is then very broad, and the regulation at least implies that drug manufacturers have a duty to be aware of off-label uses for their products and to revise the labeling as necessary to keep up with those uses.¹¹³

¹⁰⁶ Weeks, *supra* note 66, at 656. See also *supra* notes 29-37 (describing the 1938 FDCA).

¹⁰⁷ 21 U.S.C. § 355(b)(1)(E) (2008).

¹⁰⁸ *Id.* § 355(d)(1).

¹⁰⁹ 185 F.2d 321 (9th Cir. 1950).

¹¹⁰ 21 C.F.R. § 201.128 (2008).

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ Hayes, *supra* note 67, at 61; Weeks, *supra* note 66, at 657.

Until the Drug Efficacy Amendments, the Federal Trade Commission (FTC) had jurisdiction to oversee the advertising of drugs.¹¹⁴ However, testimony from physicians that drug companies were over selling the benefits of their products while failing to reveal the adverse reactions, side effects, and other negative consequences of the drugs in their advertising made it clear that the FTC had been ineffectual in controlling prescription drug advertising.¹¹⁵ As a result, Congress gave the FDA jurisdiction over advertising of drugs in 1962 stressing the importance of full disclosure.¹¹⁶

Armed with jurisdiction over advertising of prescription drugs, the FDA promulgated regulations requiring that drug manufacturers advertise drugs only for the uses and conditions for which they have been deemed safe and effective.¹¹⁷ Drug manufacturers may not make claims in advertisements that are not fully supported by substantial evidence for effectiveness. And any promotion of drugs for indications other than those for which they have approved labeling misbrands the drug.¹¹⁸ Thus, any claim made in an advertisement or promotion of any kind must be “wholly consistent with the approved product labeling.”¹¹⁹

The FDCA does not define advertisement, however, the FDA regulations on advertisements include “advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone

¹¹⁴ *Id*; see also Lars Noah, *Advertising Prescription Drugs to Consumers: Assessing the Regulatory and Liability Issues*, 32 GA. L. REV. 141, 145 (1997).

¹¹⁵ Hayes, *supra* note 67, at 61; Weeks, *supra* note 66, at 657; Charles J. Walsh & Alissa Pyrish, *FDA Efforts to Control the Flow of Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 SETON HALL L. REV. 1325, 1339-43 (1994).

¹¹⁶ Hayes, *supra* note 67, at 61; Weeks, *supra* note 66, at 657; Walsh & Pyrish, *supra* note 115, at 1339-43.

¹¹⁷ 21 C.F.R. § 202.1(e)(4)(b)(1)-(3) (2008). See also Hayes, *supra* note 67, at 61; Helm, *supra* note 19, at 151.

¹¹⁸ Hayes, *supra* note 67, at 61.

¹¹⁹ Helm, *supra* note 19, at 151.

communication systems.”¹²⁰ The regulations further proclaim that any communication or material which in any way describes the drug issued by or on behalf of the manufacturer, packer, or distributor of the drug are subject to the labeling requirements of the FDCA.¹²¹ Thus, under the 1962 Act and subsequent regulations, the FDA regulates and controls the dissemination of almost all information about drugs on the market. For many years, the FDA maintained a complete ban on the dissemination of information by manufacturers about any uses of drug for which there was not approved labeling. However, these bans were not without challenges from manufacturers.

2. *FDA Guidance on Off-Label Marketing*

In the late 1980s several reports were published revealing that the pharmaceutical industry had been aggressively supporting Continuing Medical Education (CME) Seminars for doctors and had been using these seminars as a means to promote off-label as well as off-label uses of drugs.¹²² Specifically, the reports noted changes in drug prescribing patterns, which they concluded, were linked to the increasing pharmaceutical company support of the CMEs. As a result of these reports, Congress conducted hearings to examine the effect of the pharmaceutical sponsorship of the CMEs and determined that the seminars were widely being used to promote unapproved uses of approved drugs to doctors as well as to tout the drugs for their approved uses.¹²³

In response to this information, the FDA looked for a way to continue the industry sponsored education seminars, which it realized were invaluable to disseminate information to

¹²⁰ 21 C.F.R. § 202.1(l)(1) (2008).

¹²¹ *Id.* § 202.1(l)(2).

¹²² Helm, *supra* note 19, at 155.

¹²³ *Advertising, Marketing, & Promotional Practices in the Pharmaceutical Industry*: Hearing Before the Subcomm. on Labor and Human Res., 101st Cong. 2, 5, 8-13 (1990); see also *id.*

doctors about approved drug uses, while still restricting drug companies from widespread dissemination about off-label uses. To accomplish this end, the FDA published three Guidance Documents to discourage pharmaceutical companies from promoting their products off-label through CMEs and other unregulated means such as distributing articles from medical journals discussing off-label uses to doctors and other healthcare providers.¹²⁴ In the first two Guidance Documents, the FDA recognized the legitimacy of dissemination of articles and reference guides describing the approved drug uses. However, the FDA noted that such articles might also mention unapproved uses of the drugs. The Guidance Documents made clear that manufactures may not “refer to or otherwise promote information in the article or text that is not consistent with the approved labeling for the product.”¹²⁵ In the last Guidance Document the FDA directly addressed the pharmaceutical supported educational and scientific activities such as the CME programs. The Guidance permitted the educational programs to continue, but attempted to limit their content to discussions which were not primarily promotional and were not influenced substantively by the pharmaceutical company that supported the program.¹²⁶ Further, the Guidance Document expanded the definition of “promotional relationship” so that it encompassed almost every communication between representatives from the pharmaceutical industry and healthcare workers regarding a drug’s effectiveness and use.¹²⁷

¹²⁴ Helm, *supra* note 19, at 155; Weeks, *supra* note 66, at 648.

¹²⁵ Weeks, *supra* note 66, at 648; Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data, and Guidance for Industry Funded Dissemination of Reference Texts, 61 Fed. Reg. 52,800 (Oct. 8, 1996).

¹²⁶ Weeks, *supra* note 66, at 649; Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,074-100 (Dec. 3, 1997).

¹²⁷ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,080 (Dec. 3, 1997); *see also* Helm, *supra* note 19, at 156.

3. *First Amendment Challenges to the Restrictions on Off-Label Promotion*

In 1994, the Washington Legal Foundation (“WLF”), a pharmaceutical industry supported non-profit organization, brought a First Amendment suit challenging the restrictions on the dissemination of information about unapproved uses for approved drugs outlined in the three Guidance Documents.¹²⁸ Specifically the WLF argued that the exchange of scientific information between two independent sources is constitutionally protected and therefore, the FDA cannot restrict the exchange of such information simply because it came from pharmaceutical companies.¹²⁹ They further argued that physicians needed to get reliable information about the off-label uses of drugs and the FDA restrictions were infringing on doctors’ rights to receive information.¹³⁰

The FDA countered with a two-pronged response. First, it argued that it had a duty to protect the quality of the information that doctors received about drugs. Second, it had a duty to provide manufacturers with motivation to get off-label uses approved by filing NDAs.¹³¹ The court sided with the WLF finding that the pharmaceutical companies’ promotional activities were constitutionally protected commercial speech.¹³² The court then applied the *Central Hudson* test for commercial speech and determined that the Guidance Documents were more extensive than necessary to serve the government’s two stated interests and therefore was an unconstitutional infringement on commercial speech. However, the decision was moot by the time it was handed down in 1998;¹³³ in November 1997, President Clinton signed into law the

¹²⁸ Wash. Legal Found. v. Friedman, 13. F. Supp. 2d 51 (D.D.C. 1998).

¹²⁹ *Id.* at 68. *See also* Helm, *supra* note 19, at 156; Weeks, *supra* note 66, at 649.

¹³⁰ Friedman, *supra* note 128, at 62-65.

¹³¹ *Id.* at 69.

¹³² *Id.* at 62-65.

¹³³ *Id.* at 58-59.

Food and Drug Modernization Act of 1997¹³⁴ (FDAMA), which, as the judge noted in *Friedman*, “superceded” the FDA Guidance Documents upon becoming effective.¹³⁵

The decision was still a victory for drug manufacturers as it set certain limits on how far the FDA can go in regulating the dissemination of information about off-label uses of their drugs.¹³⁶ Despite the passage of the FDAMA, the district court refused to limit its ruling to the Guidance Documents in dispute in *Friedman*. And in *Washington Legal Fund v. Henney*,¹³⁷ the FDAMA was declared unconstitutional. However, because the FDA recognized a “safe-harbor” for drug manufacturers exercising their constitutional rights in industry-supported scientific and educational activities and CME programs, this decision was ultimately vacated and the FDAMA was upheld.¹³⁸

III. THE FOOD AND DRUG MODERNIZATION ACT OF 1997

The FDAMA has been described as “the most important change in drug regulation in 20 years.”¹³⁹ It was comprehensive legislation covering a wide variety of provisions that pertained to drugs and medical devices including: changes to drug labeling requirements, growing the database on clinical trials, and expanding the fast-track approval process for AIDS and cancer drugs.¹⁴⁰ Among the many changes, the Act authorized for the first time limited authorization of

¹³⁴ The Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997). [hereinafter “FDAMA”].

¹³⁵ *Id.*

¹³⁶ Weeks, *supra* note 66, at 649.

¹³⁷ 56 F. Supp. 2d 81 (D.D.C. 1999)

¹³⁸ Wash. Legal Found. v. Henney, 202 F.3d 331, 335-37 (D.C. Cir. 2000).

¹³⁹ Weeks, *supra* note 66, at 649 (quoting Charles Marwick, *Implementing the FDA Modernization Act*, JAMA, Mar. 18, 1998, at 815).

¹⁴⁰ FDAMA, Pub. L. No. 105-115, §§ 126, 421, 113, 112. *Id.* at 649-50; FDA Backgrounder: The Modernization Act of 1997, <http://www.fda.gov/opacom/backgrounders/modact.htm> (last visited Apr. 22, 2008);

off-label marketing of drugs.¹⁴¹ “The provision seeks to balance the interests of physicians, and correspondingly of their patients to obtain legitimate information about drug uses, against FDA’s continued interest in ensuring that the manufacturers continue to study new drug effectiveness.”¹⁴²

A. STATUTORY AUTHORIZATION FOR DISSEMINATION OF INFORMATION ABOUT OFF-LABEL USES BY DRUG MANUFACTURERS

Under the FDAMA, manufacturers could disseminate authorized written materials concerning the new uses for a drug that has already been approved by the FDA to health care practitioners, pharmacy benefit managers, health insurance companies, or governmental agencies.¹⁴³ Authorized written materials were limited to unedited reprints or copies of articles appearing in a peer-reviewed scientific or medical journal or in reputable reference texts.¹⁴⁴ Manufacturers had to “prominently display” a statement with any information that they distribute to physicians stating that the information is about a use that has not been approved by the FDA, and that it was being disseminated at the manufacturer’s expense. They also had to disclose the financial interests of any authors or consultants.¹⁴⁵ Further, the manufacturers had to include the

¹⁴¹ Weeks, *supra* note 66, at 649; FDA Backgrounder: The Modernization Act of 1997, <http://www.fda.gov/opacom/backgrounders/modact.htm> (last visited Apr. 22, 2008); Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 186 (1999); Marwick, *supra* note 139, at 815; Helm, *supra* note 19, at 160; Mitchell Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1284 (2005).

¹⁴² Weeks, *supra* note 66, at 649; 21 U.S.C. § 360aaa(a)(1)-(5) (2008).

¹⁴³ 21 U.S.C. § 360aaa(b)(2) (2008).

¹⁴⁴ *Id.* at § 360aaa-1.

¹⁴⁵ *Id.* at § 360aaa(b)(6)(A)(i)-(vi).

official labeling for the drug, and information about other drugs that had been approved for the use that the information for the unapproved use describes.¹⁴⁶

Drug manufacturers that wished to disseminate information about off-label use had to first submit a copy of the information that they wish to distribute to the FDA 60 days before they start to disseminate the materials.¹⁴⁷ In addition, they had to submit any data that relates to the safety and effectiveness of the drugs for off-label uses,¹⁴⁸ and they had to submit biannual reports listing to whom they distributed the information.¹⁴⁹ Perhaps most importantly, only drug manufacturers that had submitted a SNDA for the approval of a labeling change reflecting the new use are eligible to send out this information.¹⁵⁰ And they must have either completed the efficacy studies supporting the new indication or have submitted a protocol for completing the studies within three years after the initial dissemination.¹⁵¹ Drug manufacturers that have completed the new use studies could disseminate information if they submit a certification to the FDA that they will submit a SNDA within six months of disseminating the information.¹⁵² The statute contains an exception to the required filing of the SNDA if the manufacturer can demonstrate that to do so would economically prohibitive or unethical.¹⁵³ The FDA could demand that the manufacturer stop circulating the information if it determines that the new use is not effective, risks the public health, or the manufacture fails to comply with the requirements of the Act.¹⁵⁴

¹⁴⁶ *Id.* at § 360aaa(b)(6)(A)(iv),(v).

¹⁴⁷ *Id.* at § 360aaa(b)(4)(A).

¹⁴⁸ *Id.* at § 360aaa(b)(4)(B).

¹⁴⁹ *Id.* at 360aaa-2(a)(1)-(2).

¹⁵⁰ *Id.* at § 360aaa(b)(1)(A); Weeks, *supra* note 66, at 650; Oates, *supra* note 141, at 1284.

¹⁵¹ 21 U.S.C. § 360aaa-3(a)-(c) (2008).

¹⁵² *Id.* at § 360aaa-3(b)(1)-(2).

¹⁵³ *Id.* at § 360aaa-3(d).

¹⁵⁴ *Id.* at § 360aaa-4.

B. FDA REGULATIONS FOR THE DISSEMINATION OF INFORMATION ON OFF-LABEL USES

The FDA's regulations promulgated under the FDAMA tried to balance the statute's dual goals of promoting education and the dissemination of reliable information about new uses of drugs while protecting the public from harm and trying to encourage drug manufacturers to submit SNDAs. Under the final regulations, the FDA reviewed the information to be disseminated to ensure that it is not false or misleading¹⁵⁵ and does not pose a significant health risk to the public.¹⁵⁶ Moreover, the FDA limited the types of articles that could be considered "scientifically sound" to exclude: letters to the editor; abstracts; studies about Phase I trials in healthy people; articles which do not contain sufficient substantive discussion of scientific trials; and studies with less than four subjects unless the manufacturer can demonstrate that the study would help doctors.¹⁵⁷ The regulations outlined the availability of the two exceptions to the requirement that a manufacturer file a SMDA. First, additional studies were considered economically prohibitive if additional data were necessary to support the supplemental application and if the cost of the studies was more than the expected revenue from the studies from the new use minus the expenses associated with the marketing and producing the drug for the new use.¹⁵⁸ Second, when considering whether the new studies would be unethical, the FDA considered the "degree of acceptance" of the off-label use in the medical community.¹⁵⁹ If the FDA granted an exemption for one of these two reasons, then the manufacturer could include in their biannual updates to the FDA information relating to the reason that the exemption was

¹⁵⁵ 21 C.F.R. § 99.101(a)(4) (2008).

¹⁵⁶ *Id.* at § 99.101(a)(3).

¹⁵⁷ *Id.* at § 99.101(b)(1)(i)-(v).

¹⁵⁸ *Id.* at § 99.305(c)(2)(i)-(ii).

¹⁵⁹ Weeks, *supra* note 66, at 651; 21 C.F.R. § 99.501(b)(1)-(4) (2008).

granted as well.¹⁶⁰ Outside of these provisions, the active promotion of off-label drugs was illegal.

When Congress enacted these provisions it did so with the intent of getting new treatment information into the hands of physicians while protecting patients from aggressive promotion of under-researched, dangerous, or ineffective drugs. However, few drug manufacturers took advantage of these provisions to distribute approved materials to physicians. Rather, pharmaceutical companies used the injunction issued against the FDA's guidance documents barring off-label marketing in *Friedman* and the safe harbor the FDA agreed to in *Henney* as shields under which to conduct limited off-label promotion. Consequently the FDAMA failed to have the significant impact on off-label marketing that Congress intended. And it failed to accomplish either of its objectives: establishing oversight over off-label promotion and getting reliable information about treatment options to doctors. In 2006, these provisions expired under the statute's sunset clause with little notice or fanfare.¹⁶¹ However, through the FDCA, the FDA still maintained the authority to prosecute those corporations that illegally promote their drugs off-label.

C. FDA AND DEPARTMENT OF JUSTICE ENFORCEMENT OF OFF-LABEL PROMOTION VIOLATIONS

The FDCA grants to the FDA and Department of Justice (DOJ) broad enforcement powers for violations of off-label marketing. Under the FDCA, the FDA or the Department of Justice on behalf of the FDA can bring administrative, civil, injunctive, and criminal actions against drug manufacturers for off-label marketing violations.¹⁶² The penalties can be steep

¹⁶⁰ 21 C.F.R. § 99.501(b)(5) (2008).

¹⁶¹ 21 U.S.C. §401 (e) (1998).

¹⁶² Helm, *supra* note 19, at 176; 21 U.S.C. §§ 333(a)-(b), 334.

ranging from administrative seizure of drugs, civil monetary penalties ranging from \$50,000 to \$1 million per violation, injunctive relief against promotional activities, disgorgement of profits, and criminal penalties including up to ten years in prison per violation.¹⁶³

Historically, enforcement of off-label violations was generally limited to the issuance of a public warning label followed by additional precautionary statements to drug manufacturers that were promoting drugs for off-label uses.¹⁶⁴ The public reprimand was thought sufficient to deter companies from illegally promoting the off-label uses of drugs, and so these warning labels rarely resulted in prosecutions.¹⁶⁵ However, in the past decade, the FDA and DOJ have been more aggressively enforcing misbranding and off-label violations through the use of civil and criminal actions under the FDCA.

In 1999, the DOJ criminally prosecuted a drug manufacturer for the first time for illegal off-label promotion. In that case, which resulted in \$30 million in criminal fines and \$20 million in a civil settlement, the government charged Genentech with marketing Protropin, a growth hormone for unapproved uses.¹⁶⁶ And, in 2004, Warner-Lambert agreed to a \$200 million settlement for violations under the Federal Claims Act for fraudulently marketing its drug Neurontin for off-label uses and for failing to provide adequate directions for use and introducing into interstate commerce a drug for an unapproved use under the FDCA.¹⁶⁷ Most recently, in May 2007, the DOJ prosecuted three executives and the drug company that produced Oxycontin for criminal misbranding. In that case, the DOJ argued that the executives were vicariously

¹⁶³ 21 U.S.C. §§ 333(a)-(b), 334.

¹⁶⁴ Helm, *supra* note 19, at 176.

¹⁶⁵ *Id.*

¹⁶⁶ *Id.* at 177-78.

¹⁶⁷ *Id.* See also Press Release, U.S. Department of Justice Press Release, Warner Lambert to Pay \$430 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.

liable failing to prevent or correct the introduction of Oxycontin into the marketplace for unapproved uses. The company and the executives pled guilty to the charges. The company agreed to pay more than \$100 million in civil penalties and the three executives were fined more than \$34 million in criminal fines and profit disgorgement.¹⁶⁸

Thus, the FDAMA lifted the complete ban on the dissemination of information regarding off-label uses of approved drugs. However, Congress and the FDA remained unwilling to allow manufacturers to promote the off-label uses of their drugs without requiring them to provide data supporting the safety and efficacy of the new uses. With these regulations and enforcement actions, the FDA tried to strike a balance between educating doctors and giving the public access to information about reliable drugs while still restricting drug manufacturers from overly aggressive or unethical promotion of unsafe or ineffective drugs. However, finding the appropriate regulatory and enforcement balance to best promote these often competing aims was not easy and Congress allowed the off-label promotion provisions to expire in 2006.

D. FDA DRAFT GUIDANCE OF GOOD REPRINT PRACTICES OF MEDICAL JOURNAL ARTICLES

In response to the expiration of the off-label dissemination provisions, in February 2008, the FDA released Draft Guidance outlining “its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities.”¹⁶⁹ In the Draft Guidance, the FDA recommends a system for the dissemination of

¹⁶⁸ Helm, *supra* note 19, at 179.

¹⁶⁹ Draft Guidance on Good Reprint Practices of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 73 Fed. Reg. 9342-01 (Feb. 20, 2008), *available at* <http://www.fda.gov/oc/op/goodreprint.html>.

materials describing unapproved uses that is almost identical to the off-label promotion provisions of the FDAMA. As under the FDAMA, the Draft Guidelines limit the type of materials to be distributed by manufacturers to articles published in peer reviewed, reputable scientific or medical journals.¹⁷⁰ The research supporting the articles and authors of the articles should not be published at the request of the drug manufacturers and the journal must be financially independent of the drug manufacturers.¹⁷¹ The Draft Guidance also specifies that letters to the editor, abstracts, or articles lacking substantial discussions of the research methodology should not be distributed. Articles must not discuss Phase I clinical trials and should be based on well-controlled scientifically sound clinical trials.

Also like the regulations the FDA promulgated under the FDAMA, the Draft Guidance states that manufacturers should only distribute unabridged and unedited reprints of articles.¹⁷² Along with the articles drug manufacturers must include the product's approved labeling and a bibliography of articles discussing the clinical trials and the use of the drug.¹⁷³ Manufacturers must also provide reprints of articles challenging the findings of the research the manufacturer is distributing and all of the materials must be submitted separately from any promotional materials.¹⁷⁴ Finally, manufacturers must attach a statement to the article disclosing: the uses discussed in the article are unapproved by the FDA; the manufacturer's interest in the drug; funding sources for the research discussed in the article; any financial relationship the manufacturer has with the author of the article; and any safety risks associated with the drug.

¹⁷⁰ *Id.*

¹⁷¹ *Id.*

¹⁷² *Id.*

¹⁷³ *Id.*

¹⁷⁴ *Id.*

Significantly, the Draft Guidelines do not require manufacturers to send the information to the FDA for approval prior to dissemination or require the manufacturer to submit an SNDA.

The Draft Guidance has not been finalized and is not legally binding on manufacturers. However, it reflects the current status of the law in the eyes of the FDA. More importantly, manufacturers that fail to meet the requirements of the guidance open themselves up to enforcement actions for illegal off-label promotion. Thus, if the FDA finalizes the Draft Guidance, the regulatory scheme will remain essentially the same as it was under the FDAMA.

IV. CRITIQUES OF THE OFF-LABEL MARKETING SCHEME UNDER THE FDAMA

A. THE FDA REGULATIONS OF OFF-LABEL MARKETING ARE TOO RESTRICTIVE

Critics who argue that the FDA's off-label marketing regulations and guidance are too restrictive put forth many arguments in support of their attacks on the current system. Some argue that the statute and regulations are too cumbersome and create a disincentive for drug manufacturers to disseminate information to physicians.¹⁷⁵ And others argue that the cumbersome regulations stifle innovation and disincentivize drug manufacturers from researching new uses for approved drugs.¹⁷⁶ Still, other critics argue that by restricting off-label marketing, the government is engaged in the practice of medicine and is interfering with the doctor patient relationship.¹⁷⁷ They further argue that the restrictions on off-label marketing

¹⁷⁵ See, e.g. Weeks, *supra* note 66, at 652; Salbu, *supra* note 141, at 199; Michael K. Loucks, *Pros and Cons of Off-Label Promotion Investigations and Prosecutions*, 61 FOOD & DRUG L.J. 577, 579 (2006).

¹⁷⁶ See, e.g. Oates, *supra* note 141, at 1273; Loucks, *supra* note 175, at 579; Salbu, *supra* note 141, at 198; Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 101-02 (1999).

¹⁷⁷ See, e.g. Helm, *supra* note 19, at 153; Loucks, *supra* note 175, at 579; Salbu, *supra* note 141, at 196-97.

prevent doctors from being able to have free flowing scientific exchanges that are necessary to improve patient care.¹⁷⁸ In the following sections, this paper will examine these criticisms, which focus on either the impact on physicians or the impact on research and medical innovation. While these attacks stem from different places, in the end they converge at a single overarching criticism: restrictions on the promotion of off-label uses reduce the availability of new and effective treatments and make it far more difficult for patients to receive the care they need.

1. The FDA's Off-Label Marketing Regulations Interfere with the Doctor/Patient Relationship and Prevent Doctors from Getting Valuable Treatment Information

The FDA does not regulate the practice of medicine. Doctors may prescribe any legally marketed drug for any purpose that they believe will help their patient.¹⁷⁹ Off-label uses are common in medical practice today. The precise percentage of prescriptions written off-label is unclear. Beck and Azari write that, among prescription drugs in general, those written for off-label uses “may account for more than 25% of the approximately 1.6 billion prescriptions written each year, with some recent estimates running as high as 60 percent.”¹⁸⁰ The American Medical Association and several other sources estimate that roughly half of all prescriptions are written for off-label uses.¹⁸¹ And, the General Accounting Office, in a 1996 report estimated that 90

¹⁷⁸ *Id.*

¹⁷⁹ James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 76 (1998); Helm, *supra* note 19, at 122; Salbu, *supra* note 141, at 193.

¹⁸⁰ Beck & Azari, *supra* note 179, at 80.

¹⁸¹ Veronica Henry, *Off-label Prescribing: Legal Implications*, 20 J. LEGAL MED. 365, 365 (1999); Kaspar J. Stoffelmayr, *supra* note 98, at 276.

percent of cancer drug use, 80 percent of pediatric drug use, and between 80 and 90 percent of drugs used for rare conditions are prescribed off-label.¹⁸²

Off-label uses are not only prevalent in medical practice, in many areas they are cutting edge.¹⁸³ For cancer patients, off-label treatments are generally considered to be some of the most effective treatments available. A report by the General Accounting Office called off-label use “state of the art treatment” in oncology.¹⁸⁴ Off-label uses in the treatment of HIV and AIDS have been “dramatic.”¹⁸⁵ Steven Salbu writes that “between ninety and one hundred percent of applications, including all of the revolutionary antiretroviral combination therapies, are off-label.”¹⁸⁶ Indeed, off-label uses are involved in the standard treatment of heart and circulatory disease, kidney disease, osteoporosis, spinal fusion surgery, and various uncommon diseases.¹⁸⁷

Thus, as the editor of the Journal of the American Medical Association testified before Congress in 1991, “prescribing FDA-approved drugs for off-label (unlabeled) uses often is necessary for optimal patient care.”¹⁸⁸ Congress and the FDA have recognized this.¹⁸⁹ And the only check on physicians’ power to prescribe off-label is the potential for tort liability and

¹⁸² GENERAL ACCOUNTING OFFICE, PRESCRIPTION DRUGS: IMPLICATIONS OF DRUG LABELING AND OFF-LABEL USE, [T-HEHS-96-212](#) [hereinafter “GAO REPORT PRESCRIPTION DRUGS”].

¹⁸³ *Id.* See also Beck & Azari, *supra* note 179, at 80; GENERAL ACCOUNTING OFFICE, REPORT TO THE CHAIRMAN, COMM. ON LABOR AND HUMAN RESOURCES, U.S. SENATE, OFF-LABEL DRUGS: REIMBURSEMENT POLICIES CONSTRAIN PHYSICIANS IN THEIR CHOICE OF CANCER THERAPIES 11 (1991) [hereinafter “GAO REPORT OFF-LABEL DRUGS”].

¹⁸⁴ GAO REPORT CANCER THERAPIES, *supra* note 183, at 11. See also Beck & Azari, *supra* note 179, at 80; Salbu, *supra* note 141, at 193.

¹⁸⁵ Salbu, *supra* note 141, at 194; see also Salbu, *supra* note 176, at 102-11.

¹⁸⁶ Salbu, *supra* note 141, at 194.

¹⁸⁷ Beck & Azari, *supra* note 179, at 80.

¹⁸⁸ *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Human Resources and Intergovernmental Relations Subcomm. of the House Comm. on Gov’t Operations*, 102d Cong., 1st Sess. 103 (1991) (statement of George Lundberg, M.D.). See also Beck & Azari, *supra* note 179, at 79.

¹⁸⁹ See *Use of Unapproved Drugs for Unlabeled Indications*, *supra* note 96.

“gradually dwindling vestiges of insurance company and health plan policies that deny coverage of off-label applications, where such policies are still legal.”¹⁹⁰

However, physicians must be aware of the off-label treatments in order to prescribe them to their patients. Many critics of the FDA regulations argue that the restrictions on off-label marketing thwart the access of patients who could have benefited from these drugs had only their doctors been aware of their off-label uses.¹⁹¹ These critics make two main attacks: first, they argue that the restrictions prevent doctors from receiving reliable information about new uses; and second, they argue that the regulations intrude upon the doctor patient relationship.

a. The Regulations Prevent Doctors from Getting Information About New Uses

Doctors rely primarily on drug manufacturers to learn about drugs for their approved uses.¹⁹² In some cases, drug manufacturers may provide doctors with information about the off-label uses of certain drugs. However, because drug manufacturers must endure significant costs, such as supplemental clinical trials and increased reporting costs, critics argue that under the current regulations it is simply not cost effective for many drug manufacturers to send doctors information about off-label uses. Many doctors then are not receiving information from drug manufacturers about potential treatments that could benefit their patients.¹⁹³

Even when they are permitted to disseminate information to doctors, drug manufacturers may only send full reprints of articles from peer reviewed medical or scientific journals. For off-

¹⁹⁰ *Salbu*, supra note 141, at 194.

¹⁹¹ *Salbu*, supra note 141, at 194; Helm, supra note 19, at 122, 171.

¹⁹² Charles Walsh & Alissa Pyrish, *FDA Efforts to Control the Information at Pharmaceutical Industry-Sponsored Medical Education Programs: A Regulatory Overdose*, 24 SETON HALL L. REV. 1325, 1330-31 (1994); Weeks, supra note 66, at 647; Helm, supra note 19, at 122.

¹⁹³ *Salbu*, supra note 141, at 194-95; Helm, supra note 19, at 122, 171; Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 980 (2007).

label uses doctors, then, must get their information either from medical literature¹⁹⁴ or informally through their peers.¹⁹⁵

Doctors, who spend most of their days seeing patients, do not have time to keep up with all of the medical literature. When sponsoring legislation to reduce the restrictions on off-label marketing, Senator Bill Frist, a former heart surgeon, said: “If a conscientious doctor were to read two medical articles before retiring each night, he would have fallen 550 years behind in his reading at the end of the first year.”¹⁹⁶ By limiting the means through which doctors can obtain information to journal articles, the FDA regulations then limit not only the type of information but also the amount of information that doctors can get.

Doctors have always been allowed to get information from each other informally. However, critics, including doctors and other medical groups, have long argued that these informal channels are insufficient. In 1997, the American Medical Association made it one of its policy goals to

“seek to persuade FDA to ensure physicians have greater access to information about unlabeled (off-label) uses of medications citing the prevalence and clinical importance of prescribing drugs for unlabeled uses . . . and the critical need for physicians to have access to accurate and unbiased information about unlabeled uses of prescription drugs.”¹⁹⁷

¹⁹⁴ Though manufacturers who have submitted a SNDA and gotten approval from the FDA may disseminate information to doctors about off-label uses. However, they may only send full reprints of articles printed in a scientific or medical journal. *See supra* notes 144-151 (discussing the FDA’s regulations for distribution of material for off-label uses).

¹⁹⁵ *Salbu*, *supra* note 141, at 194-95; *Helm*, *supra* note 19, at 122, 171; *Johns*, *supra* note 193, at 980.

¹⁹⁶ James O’Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 303 (2003).

¹⁹⁷ Beck & Azari, *supra* note 179, at 103 (quoting *AMA Supports Greater Physician Access to Unlabeled Use Information*, STANDARD, July 1997, available at <http://www.usp.org/pubs/standard/97jul/ama.htm>) (internal quotations omitted).

Without access to information about off-label uses, doctors will have very little information to share.

Salbu argues that doctors will notice trends and develop theories about effective off-label treatments that they will test informally in their practices.¹⁹⁸ He maintains that, for doctors involved in large networks, these informal findings can be a “likely source of some innovative drug applications.”¹⁹⁹ However, doctors who are practicing as sole practitioners or who lack a large network to tap into will not be able to obtain this information.²⁰⁰ Moreover, while there is value in the information developed and shared in these informal networks, it is merely anecdotal; in order for it to have a widespread impact on patient treatment, it must be formally tested and broadly shared across the medical community. “Manufacturers have the greatest incentive, as well as resources, to spread the news of research findings that support new and beneficial off-label uses of their products. Liberalized off-label promotion therefore should yield the most progressive medical practice.”²⁰¹

b. The FDA’s Regulations Intrude on the Doctor Patient Relationship

Some critics assert that limiting doctors’ access to information in this way interferes with the doctor patient relationship. Doctors are in the best position both to evaluate the needs of their patients and evaluate the available treatment options.²⁰² The reason that we have such few regulatory controls on doctors is because we want them to be able to assess patients’ individual needs and tailor a treatment plan to meet those needs.²⁰³ “This professional autonomy is

¹⁹⁸ *Salbu*, supra note 141, at 197.

¹⁹⁹ *Id.*

²⁰⁰ *Id.*

²⁰¹ *Id.* at 199.

²⁰² See, e.g., Helm, supra note 19, at 122, 167; Mark Ford, Note, *Another Use of Oxycontin: The Case for Enhancing Liability for Off-Label Drug Marketing*, 83 B.U. L. REV. 429, 433 (2003).

²⁰³ Helm, supra note 19, at 119-20.

considered the cornerstone of medical practice.”²⁰⁴ And, it is the reason we allow, and at times, encourage doctors to prescribe drugs off-label. “Once it is accepted that off-label uses are desirable, it is difficult to maintain that doctors should be shielded from truthful information concerning how to use a product for an off-label use. Patients will benefit from having their doctors informed about off-label uses.”²⁰⁵

Unlike patients who have little scientific background, doctors are able to evaluate the information they receive from pharmaceutical companies about the drugs they prescribe, and so the FDA should be less concerned about them being misled or confused by communications from drug manufacturers.²⁰⁶ Doctors are fully aware of the FDA’s drug approval process and know the risks for off-label prescription. Moreover, under the learned intermediary doctrine, doctors bear the risk of prescribing a drug off-label through tort law so they may as well have all of the information necessary to make the best decisions for their patients.²⁰⁷ “Good decisions are made with as much information as possible. Good healthcare decisions likewise should be made with as much data on the use of drugs for non-approved indications as possible.”²⁰⁸ By preventing doctors to get information about off-label uses, the FDA is preventing physicians and patients from being able to make informed and impartial decisions.²⁰⁹

²⁰⁴ *Id.* at 119.

²⁰⁵ *In re Orthopedic Bone Screw Prod. Liab. Litig.*, 159 F.3d 817, 831 (3d. Cir. 1998) (Cohen, J., dissenting), rev’d, *Buckman Co. v. Plaintiff’s Legal Comm.*, 531 U.S. 341 (2001). *See also* Weeks, *supra* note 66, at 648.

²⁰⁶ Paul H. Rubin, *From Bad to Worse: Recent FDA Initiatives and Consumer Health*, in *BAD PRESCRIPTION FOR THE FIRST AMENDMENT* 87, 91 (Richard T. Kaplar ed., 1993).

²⁰⁷ Helm, *supra* note 19, at 167-69; Ford, *supra* note 202, at 433-35; O’Reilly & Dalal, *supra* note 196, at 324.

²⁰⁸ Helm, *supra* note 19, at 167.

²⁰⁹ Helm, *supra* note 19, at 121.

2. *The FDA's Off-Label Marketing Regulations Stifle Innovation and Create Disincentives for Manufacturers to Develop and Disseminate Useful Information to the Medical Field*

Given the prevalence of off-label practices in modern medicine, it is important to know if these treatments are safe and effective.²¹⁰ To garner the relevant data and information, research about off-label uses must continue even after the FDA has granted approval for a drug. While pharmaceutical research takes place in a variety of settings including government laboratories, universities, and non-profit research centers,²¹¹ the majority of pharmaceutical research in this country is funded and conducted by drug manufacturers.²¹² However, the FDA regulations do not currently require companies to conduct this research if they do not wish to send doctors articles on the off-label uses of their drugs; given the cost of conducting this research, critics argue that most manufacturers will not likely undertake this research.²¹³ Some manufacturers might decide to research off-label uses, but “whether this occurs will depend upon the economic incentives involved, and there is reason to believe that these incentives are less than robust.”²¹⁴

Thus, rather than incentivize pharmaceutical companies to conduct research into off-label uses of pre-approved drugs, the FDA's regulations are overly cumbersome and make it financially unfeasible for drug companies to conduct this research. Even if it is financially feasible for the company to conduct the research, the costs of doing so are particularly high and get passed onto the consumer. These critics typically cite three reasons why the regulations disincentive research: first, the drug manufacturers cannot widely disseminate information about off-label uses; second, the SNDA process is too cumbersome and expensive; and third, the drug manufacturers' competitors benefit more from their research than they do.

²¹⁰ Oates, *supra* note 141, at 1274.

²¹¹ Salbu, *supra* note 141, at 198.

²¹² *Id.*

²¹³ Oates, *supra* note 141, at 1274; *See also* Weeks, *supra* note 66, at 652; Salbu, *supra* note 141, at 198-99; Salbu, *supra* note 176, at 102; Loucks, *supra* note 175, at 579.

²¹⁴ Oates, *supra* note 141, at 1274.

a. Drug manufacturers cannot widely disseminate information about off-label uses

“Production of knowledge about pharmaceutical products is the central objective of pharmaceutical research and development, supplemented by substantial public section expenditures for medical research and the activities of a wide array of clinicians and academicians. Before that knowledge constitutes useful information, however, it must be disseminated to the practitioners who can use it. Dissemination of pharmaceutical information is an industry unto itself, involving medical journals, textbooks, consensus conferences under governmental auspices, and substantial manufacturer expenditures on promotion. Thus, pharmaceutical research and development and pharmaceutical promotion are complementary activities.”²¹⁵

If drug manufacturers cannot promote the information revealed by their research, they have no reason to conduct the research. By banning off-label promotion, the FDA significantly reduces drug manufacturers’ incentives to research new uses for already approved drugs.²¹⁶ A substantial portion of a drug’s market share can come from off-label sales.²¹⁷ And drug manufacturers may be motivated to research a drug’s off-label uses if they can widely publicize the new uses of their products in order to increase sales of a drug. However, due to the FDA marketing regulation, drug manufacturers are unlikely to reach the number of physicians and health care workers that they would need to reach in order to increase their sales significantly.²¹⁸ Since drugs can often achieve significant sales for off-label uses without any formal research substantiating the efficacy of the drug for the new use,²¹⁹ the marginal increases in sales that companies may be able to get by sending FDA approved materials to a limited number of

²¹⁵ J. Howard Beales III, *Economic Analysis and the Regulation of Pharmaceutical Advertising*, 24 SETON HALL L. REV. 1370, 1370 (1994).

²¹⁶ Oates, *supra* note 141, at 1274-75; Salbu, *supra* note 141, at 199; Loucks, *supra* note 175, at 579; Edmund Polubinski III, *Closing the Channels of Communication: A First Amendment Analysis of the FDA’s Policy on Manufacturer Promotion of “Off-Label” Use*, 83 VA. L. REV. 991, 993 (1997). See generally Beales, *supra* note 215.

²¹⁷ David C. Radley, et al., *Off-Label Prescribing Among Office Based Physicians*, 166 Arch. Internal Med. 1021, 1023 (2006); Helm, *supra* note 19, at 152-53.

²¹⁸ Oates, *supra* note 141, at 1274-75; Salbu, Oates, *supra* note 141, at 1274; Loucks, *supra* note 175, at 579; Polubinski, *supra* note 216, at 993.

²¹⁹ Radley, *supra* note 217, at 1023; Helm, *supra* note 19, at 152-53.

physicians are insufficient to justify the significant costs of research.²²⁰ And to be eligible to disseminate these very limited materials about new uses to physicians drug manufacturers must submit a SNDA to the FDA, which is a demanding and costly process.²²¹

Further, the risk of undertaking clinical trials is high because there is a chance that the trials may reveal a negative result.²²² Thus, given the high cost and high risk of the trials, drug manufacturers are not likely going to undertake new trials unless they could significantly increase the drug's sales. The increased sales projections are depressed by the FDA's restrictions on off-label promotion.

Elizabeth Weeks argues that drug manufacturers who send information to physicians about new uses open themselves up to regulatory sanctions if they fail to meet the FDA's complicated policy on dissemination. The recent DOJ investigations and prosecutions for off-label promotions further increase the risks to drug manufacturers. These "increased regulatory scrutiny and potential sanctions may provide disincentives for manufacturers to avail themselves of the approved dissemination option. Instead, they may continue to rely on unapproved or underground dissemination, such as informal communication among doctors or unsponsored studies published in journals, that does not carry the same threat of sanctions."²²³

b. FDA's Supplemental New Drug Application Process is Cumbersome and Expensive

Weeks also argues that in addition to the limitations on disseminating information about new research, drug manufacturers may not research new uses for approved drugs because the process of having a new use recognized by the FDA is too cumbersome and costly. To have

²²⁰ Oates, *supra* note 141, at 1274-75; Salbu, *supra* note 141, at 199; Polubinski, *supra* note 216, at 993; Weeks, *supra* note 66, at 652.

²²¹ *Id.* at 652. See *supra* notes 38-43 (discussing the SNDA process).

²²² Oates, *supra* note 141, at 1274.

²²³ Weeks, *supra* note 66, at 662.

more than one use approved for a drug, the manufacturer must submit an SNDA. The SNDA process can be even more expensive than the original NDA process because drug manufacturers have to submit new Phase II and III data about efficacy, which are the most expensive studies to run, and the FDA gives supplemental applications lower priority than original approvals so they may take longer. While the FDA regulations except pharmaceutical companies from having to submit SNDAs for economic hardship, the FDA has made it clear that it will not grant these exemptions liberally.²²⁴

When submitting a drug for original approval, drug manufacturers will usually submit a NDA for a minimal number of uses to get their drug to market as quickly as possible.²²⁵ If they have reason to believe that there may be an unapproved use for their drug, they can sponsor a study of the drug, the results of which will be made public in a medical or scientific study.²²⁶ This study does not have to meet the stringent methodological standards of an FDA approved study however.²²⁷ The only incentive then that manufacturers have to submit an SNDA is to be able to send articles directly to physicians or to change the labeling so that they can promote the drug for the new use. As discussed above, the ability to send the article to doctors directly rather than waiting for doctors to discover the published article on their own, will likely not increase sales enough to make the increased costs of vigorous research and administrative delay worthwhile. While a labeling change could allow manufacturers to significantly increase

²²⁴ *Id.*

²²⁵ *Id.* at 663; John E. Calfee, *Free Speech, FDA Regulation, and Market Effects on the Pharmaceutical Industry*, in *BAD PRESCRIPTION FOR THE FIRST AMENDMENT*, *supra* note 206, at 69.

²²⁶ Weeks, *supra* note 66, at 663; Rubin, *supra* note 206, at 91.

²²⁷ Weeks, *supra* note 66, at 663.

product sales, the fact that generic drugs also benefit from the labeling change reduces the original manufacturer's expected profits from the new use substantially.²²⁸

C. DRUG MANUFACTURERS' COMPETITORS BENEFIT MORE FROM THEIR RESEARCH THAN THEY DO

The Drug Price Competition and Patent Term Restoration Act of 1984 significantly eroded patent protection for new drugs allowing generic drug manufacturers to make a generic version of a drug while the original drug manufacturer's patent was still in force.²²⁹ The Act also accelerated the FDA's approval of generic drugs.²³⁰ Katherine Helm argues that early entry of pharmaceutical drugs gives patients access to cheaper drugs, but it also means that the original drug manufacturers have less incentive to seek FDA approval for a new use.²³¹

Once a generic version of a drug enters the marketplace for the first approved use, it will be prescribed for all on- and off-label uses.²³² Moreover, many states have laws requiring physicians to prescribe and pharmacists to dispense available generic versions of drugs for all on and off-label uses for which it is prescribed. Many of these state laws prohibit insurance companies from refusing to reimburse generics that are prescribed off-label just because they are prescribed for an off-label use.²³³ And, federal Medicare policies cover off-label uses that are considered medically acceptable.²³⁴ Thus, according to Helm, if a drug manufacturer submits a

²²⁸ Helm, *supra* note 19, at 164-67; Loucks, *supra* note 175, at 580; Weeks, *supra* note 66, at 664.

²²⁹ Merrill, *supra* note 5, at 1792; Helm, *supra* note 19, at 143-44. The full effect of the Drug Price Competition and Patent Term Restoration Act is beyond the scope of this paper. For a detailed discussion of the Act and its implications see Merrill, *supra* note 5, at 1792-94.

²³⁰ Merrill, *supra* note 5, at 1792; Helm, *supra* note 19, at 143-44.

²³¹ Helm, *supra* note 19, at 164.

²³² *Id.*

²³³ *Id.* at 164-65.

²³⁴ *Id.* at 165.

SNDA for a new use, any new market they create from the new use is able to substitute the generic for the original drug as soon as a generic is available. Since it would be the same if the manufacturer did not submit the SNDA, there is little incentive for a drug manufacturer to invest in the application. “In sum, off-label uses are highly profitable for pharmaceutical manufacturers prior to generic entry, and are highly profitable for generic manufacturers thereafter.”²³⁵ Moreover, because generic drugs can come to market so quickly and the SNDA approval process takes such a long time, drug manufacturers will have only a small window in which to reap profits from any new uses for which they get FDA approval.²³⁶

B. FDA REGULATIONS OF OFF-LABEL MARKETING ARE INADEQUATE TO PROTECT PATIENTS

“Before the FDAMA was adopted, the FDA asserted that permitting drug companies to promote off-label use would remove incentives to obtain definitive clinical study data, weaken the goal of evidence-based medicine, erode the drug efficacy requirements, and harm patients by unstudied uses that actually lead to bad results or that are merely ineffective.”²³⁷ Those arguing for tighter restrictions on off-label marketing essentially make the same arguments today.²³⁸ An examination of these criticisms reveals that no matter how varied they all appear, they all ultimately make the same basic objection: the lack of regulatory and governmental control over the promotion and use of off-label uses “endangers human health and human life.”²³⁹

²³⁵ *Id.*

²³⁶ *Id.*; Weeks, *supra* note 66, at 663.

²³⁷ O’Reilly & Dalal, *supra* note 196, at 305. See also Janet Woodcock, M.D., Lecture to Drug Information Association, *A Shift in the Regulatory Approach* (June 23, 1997), available at <http://www.fda.gov/cder/present/diamontreal/regappr/sld001.htm>.

²³⁸ See Salbu, *supra* note 141, at 201; O’Reilly & Dalal, *supra* note 196, at 305-09.

²³⁹ Salbu, *supra* note 141, at 201.

1. FDA's Regulations Discourage Drug Manufacturers from Researching the Safety and Efficacy of New Uses

Critics such as James O'Reilly, Amy Dalal, and Karen Bradshaw argue that the FDAMA's relaxation of the off-label promotion restrictions removed any real incentive for drug manufacturers to conduct the rigorous clinical trials necessary to demonstrate the safety and efficacy of their product for off-label uses.²⁴⁰ Doctors can learn of the off-label uses of drugs through informal networks and manufacturers can sell their products for off-label uses without having to expend the resources to prove the product is safe and effective. They, therefore, have little incentive to invest in the expensive research required to relabel the product to reflect the new indication.²⁴¹ Moreover, manufacturers have little incentive to research a drug that is already selling well for off-label uses because they could discover that the drug is unsafe and be forced to pull it from the market.²⁴²

Even under the current regulations, some manufacturers will not research off-label uses after a drug has been approved. However, critics argue that unless the FDA monitors these studies, they are at best ineffective at promoting safety and efficiency for two reasons. First, manufacturers will likely conduct less scientifically rigorous trials than they would be required to perform under the FDA's standards because they are less expensive and because they may produce a more favorable result. Even though these studies have not met the methodological standards that the FDA requires to demonstrate safety and effectiveness, the manufacturer will nevertheless be able to publicize the results by publishing them in a widely read medical journal

²⁴⁰ O'Reilly & Dalal, *supra* note 196, at 307. Karen Bradshaw, *The Food and Drug Administration Modernization and Accountability Act of 1997: Is it the Answer to the Off-Label Advertising Debate?* (1998), <http://leda.law.harvard.edu/leda/data/226/kbradshaw.pdf> (last visited May 5, 2008).

²⁴¹ O'Reilly & Dalal, *supra* note 196, at 307; Salbu, *supra* note 141, at 205-06.

²⁴² O'Reilly & Dalal, *supra* note 196, at 307; Bradshaw, *supra* note 240, at 18.

that will reach physicians and healthcare workers.²⁴³ Doctors and others who hear of the news may thus think that the drug is reliable and safe for the new indication even though the study may not demonstrate that to the FDA's standards.

Second, the FDA regulations do not require manufacturers to reveal the results from clinical trials. Manufacturers who discover results that may be damaging to sales are unlikely to reveal them to the public.²⁴⁴ Michael Oates argues that this failure to require manufacturers to reveal clinical trial results to the public even if they are not conducted under FDA review is a huge shortcoming of the regulatory scheme.²⁴⁵

2. FDA's Regulations Encourage Drug Manufacturers to Bypass its Review Process

Critics also note that the ability of manufacturers to sell and market drugs off-label is a disincentive to bypass FDA review even before a drug has gotten to market. As noted above, drug companies can often achieve significant sales for off-label uses.²⁴⁶ These sales are particularly profitable because the drug company did not have to get FDA approval for the use and therefore did not have to expend the significant capital and time in doing so.²⁴⁷ Thus, drug manufacturers have incentives to "game the system" and push a drug through for initial approval using the minimum number of clinical trials needed to get approval for the most basic use of the drug knowing that they can still sell the drug off-label for other uses at greater profit margins.²⁴⁸ Even if they cannot "promote the drug" directly to physicians under the current regulations,

²⁴³ Weeks, *supra* note 66, at 663; Rubin, *supra* note 206, at 91.

²⁴⁴ Oates, *supra* note 141, at 1272.

²⁴⁵ *Id.*

²⁴⁶ Radley, *supra* note 217, at 1023; Helm, *supra* note 19, at 152-53.

²⁴⁷ Helm, *supra* note 19, at 152-53.

²⁴⁸ O'Reilly & Dalal, *supra* note 196, at 306-07. Note, this is the same consequence that Weeks and others pointed to as evidence that the guidelines were too stringent. Weeks, *supra* note 66, at 663. See *supra* notes 223-225 and related discussion.

pharmaceutical companies have found pretextual ways to “advertise” their drug to doctors. As Marcia Angell wrote in her book, The Truth About Drug Companies, drug companies use professional education courses to promote drugs off-label:

“You do that by carrying out ‘research’ that falls way below the standard required for FDA approval, then educating doctors about favorable results. That way you can circumvent the law. You could say you were not marketing for unapproved uses; you were merely disseminating the results of research to doctors . . . But it would be bogus education about bogus research. It would really be marketing.”²⁴⁹

Even though this so called marketing that Dr. Angell describes in her book may be prohibited, the FDA lacks the resources to effectively regulate this behavior and even more blatant violations of the ban on off-label promotion.²⁵⁰ It can thus do little to stop manufacturers who use impermissible channels and means to promote the off-label uses of their drugs.²⁵¹

3. FDA’s Regulations Allow Drug Manufacturers to Treat Patients Like Guinea Pigs

a. FDA’s Regulations Allow Experimental Drugs into the Marketplace

Because drugs being prescribed off-label have not undergone FDA review for the new uses, some critics argue that drugs prescribed off-label are essentially the same as experimental drugs.²⁵² Public Citizen, a consumer advocacy group, asserted that by loosening the off-label marketing restrictions, the FDAMA forces patients to “become part of an uncontrolled experiment where no one is keeping track of who’s helped and who’s hurt.”²⁵³

²⁴⁹ MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES* 204 (2004). *See also* Johns, *supra* note 193, at 988.

²⁵⁰ O’Reilly & Dalal, *supra* note 196, at 306-07.

²⁵¹ *Id.*

²⁵² *Id.* at 305-06; Salbu, *supra* note 141, at 205-06; Jaime A. Wilsker, Note and Comment, *One-Half Phen in the Morning/One Fen Before Dinner: A Proposal for FDA Regulation of Off-Label Uses of Drugs*, 6 J.L. & POL’Y 795, 844 (1998).

²⁵³ *FDA to Ease “Off-Label” Use Restrictions*, HEALTH LINE, June 8, 1998. *See also* Salbu, *supra* note 141, at 204.

Public Citizen and other critics argue that a primary purpose of the FDA review of new drugs is to determine not only the safety of the drug, but also the proper dosage for a given use and potential side effects and risks at that dosage.²⁵⁴ Drugs that are being used off-label have not necessarily been tested at the dosage at which they are being prescribed, or for interactions with certain drugs, or in the population to whom they are being prescribed. Thus, from a patient safety perspective, in these situations off-label drugs are indistinguishable from unapproved drugs that have also not been scrutinized in these ways.²⁵⁵

b. FDA's Regulations Fail to Inform Their Patients When Their Doctor Prescribes Them a Drug Off-Label

Margaret Johns, in her article *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, faults the FDA's regulations for failing to force doctors to tell patients when they are prescribing a drug off-label.²⁵⁶ In this way she argues that patients are unwittingly subject to the risk of taking "investigational" medications.²⁵⁷ Johns maintains that the FDA's regulations give doctors too much autonomy in making decisions for patients and do not adequately protect patients from doctors who may have been influenced by drug company marketing.²⁵⁸ She argues that when a patient receives a prescription from her doctor, she assumes mistakenly that the drug has been found safe and effective according to the FDA's standards. Since the patient is ultimately the one bearing the risk of taking a drug that has not been fully tested, Johns argues that the patient should be able to make a fully informed decision about whether to take the risk. Thus she argues that the drug's off-label status should be

²⁵⁴ Salbu, *supra* note 141, at 204.

²⁵⁵ *Id.* Wilsker, *supra* note 252, at 844-45.

²⁵⁶ See Johns, *supra* note 193, at 1012-13.

²⁵⁷ *Id.* at 1017.

²⁵⁸ *Id.* at 1012-13.

disclosed to the patient because “surely patients would want to know the doctor’s basis for recommending an off-label treatment.”²⁵⁹

V. POPULAR “SOLUTIONS” AND SUGGESTED REFORMS TO THE OFF-LABEL PROMOTION REGULATIONS

Scholars and practitioners have suggested a variety of solutions to address these and other criticisms of the off-label marketing system. In fact, the academic literature on FDA's off-label marketing regulations is replete with proposals for how to better maximize patient access to effective and affordable treatments, promote research and innovation, and protect patients from unsafe drugs. Authors have suggested solutions ranging from complex guidelines for the FDA to employ when considering whether to impose rigid or strict research requirements for off-label uses to tax reforms. However, the most commonly suggested changes are: deregulation of off-label promoting;²⁶⁰ legally mandated informed consent;²⁶¹ changing FDA policies and procedures;²⁶² and, patent reform.²⁶³ Whether the changes are sweeping or minor, a close examination of each of them reveals that they are at best ineffective and, in some cases, would cause more harm than good.

A. DEREGULATING OFF-LABEL PROMOTION

Scholars such as J. Howard Beales, John Calfee, Paul Rubin, Steven Salbu, Edmund Polubinski, Charles Walsh, Alissa Pyrish, and others have argued that the regulation and

²⁵⁹ *Id.* at 1019.

²⁶⁰ *See, e.g.,* Beales, *supra* note 215; Calfee, *supra* note 225; Rubin, *supra* note 206; Salbu, *supra* note 141; Polubinski, *supra* note 216; Walsh & Pyrish, *supra* note 115.

²⁶¹ *See, e.g.,* Johns, *supra* note 193.

²⁶² *See, e.g.,* Weeks, *supra* note 66, at 663; Oates, *supra* note 141; Helm, *supra* note 19.

²⁶³ *See, e.g.,* Helm, *supra* note 19. Patent reform is beyond the scope of this paper and so it will not address it. However, I mention it here simply because it appears frequently in the literature as an area for possible reform.

restriction of off-label marketing slows medical innovation and prevents doctors and patients from getting the information they need to make well-informed treatment decisions.²⁶⁴ Some of these scholars advocate complete deregulation of off-label promotions and others prefer only partial deregulation. They all agree, however, that keeping pharmaceutical companies from disseminating “truthful information” to doctors about the potential off-label uses of their products has “thwarted the access of [patients]” to potential life-saving and life-improving treatments.²⁶⁵

These critics contend that market forces, rather than regulation will best minimize the risks associated with off-label use. Moreover, market forces will better support the rapid dissemination of valuable information to doctors and patients.²⁶⁶ Even without FDA oversight, drug manufacturers will not act irresponsibly by promoting drugs they know are dangerous or ineffective for fear of reputational repercussions and tort litigation. Even if this deregulation would sacrifice some degree of protection “the invaluable benefits of off-label practices outweighs some loss in the preservation of public safety from unproven applications.”²⁶⁷ In the aggregate, by getting more information about treatments to more patients, deregulation would save more lives than the complex protectionist scheme currently in place.²⁶⁸

Some scholars advocate for partial deregulation. Steven Salbu argues for keeping the restriction on off-label marketing to physicians and healthcare professionals as well as the

²⁶⁴ See Beales, *supra* note 215; Calfee, *supra* note 225; Rubin, *supra* note 206; Salbu, *supra* note 141; Polubinski, *supra* note 216; Walsh & Pyrish, *supra* note 115; Stoffelmayr, *supra* note 98, at 287.

²⁶⁵ Salbu, *supra* note 141, at 199, 195 n. 86; Walsh & Pyrish, *supra* note 115, at 1354 n. 158.

²⁶⁶ See, e.g., Salbu, *supra* note 141, at 219; Beales, *supra* note 215, at 1370-72.

²⁶⁷ Salbu, *supra* note 141, at 219.

²⁶⁸ *Id.*; Beales, *supra* note 215, at 1370-72; Polubinski, *supra* note 216, at 1029; Walsh & Pyrish, *supra* note 115, at 1361-62.

disclosure requirements.²⁶⁹ He suggests supplementing the deregulated system with mandated informed patient consent and tort reform to make manufacturers responsible for the negligent promotion of unsafe drugs and for dishonest or inaccurate marketing of off-label uses.²⁷⁰

Polubinski focuses on protecting First Amendment rights. He proposes a requirement that drug manufacturers promoting drugs off-label be required to disclose: the manufacturers interest in the promotional activity and support it provided to the research, the extent to which the treatments being promoted constitute unapproved uses, and the official labeling of the drugs to recipients of educational support or written materials.²⁷¹

Elizabeth Weeks suggests liberalizing the current restrictions by permitting manufacturers to send a wider variety of materials or by only requiring pre-dissemination notification rather than approval.²⁷² Similarly, Katherine Helm suggests reducing some of the SNDA requirements for already approved drugs supplemented by increased post-marketing surveillance and risk assessment.²⁷³

The appeals to deregulate off-label marketing are pleasing in theory. They play to our capitalist sensibilities and to the American ideals of a free market and innovation. However, in practice, these ideas are not only impractical but they are dangerous. Millions of Americans rely on prescription drugs everyday. And doctors need reliable information about the benefits and risks of drugs to treat their patients. The reason that jurisdiction over drug promotion was taken from the FTC and given to the FDA in 1962 was because doctors complained en masse that under the FTC's loose advertising guidelines "drug companies tended to emphasize the positive

²⁶⁹ Salbu, *supra* note 141, at 220.

²⁷⁰ *Id.* at 219-26.

²⁷¹ Polubinski, *supra* note 216, at 1031.

²⁷² Weeks, *supra* note 66, at 663. Weeks also suggest expedited review of pre-promotion materials which is discussed *infra* at Section V.C.1..

²⁷³ Helm, *supra* note 19, at 182-85.

features and advantages of the drugs but did not describe side effects, contraindications, adverse reactions, and warnings adequately.”²⁷⁴ There is no reason to believe that without adequate oversight and regulation, drug companies would not revert to these practices for off-label and on-label uses of drugs.

However, for on-label drugs, doctors would be able to find adverse information about the drug easily. For off-label uses, this information would not be available unless the manufacturer voluntarily conducted trials about the safety and efficacy of the new use. While proponents of deregulation of off-label marketing argue that loosened restrictions will stimulate research on already approved drugs to be able to capture a larger portion of the market share, this seems unlikely. Drug manufacturers have few incentives to research safety and effectiveness if they can market the drug without expending the money to do so and without risking discovery an adverse side effect.

What proponents of deregulation ignore is that drug companies could likely increase their sales as much or more by investing in advertising dollars than in detailed research about the new use. Though they may have to conduct basic research to discover if the drug has any off-label uses, it is in the drug companies best interest to keep these tests as narrow as possible so that they will not learn of any adverse side effects or contraindications that might weaken their sales. Moreover, even if a drug company invested in research about a new use, it would still then have to invest heavily in promotion to get this information out. If there is no regulation of their promotional activities, then it seems a much smarter business model to just skip the expensive and risky research and opt instead for the widespread and slick advertising campaign.

²⁷⁴ Weeks, *supra* note 66, at 657.

Proponents of deregulation of marketing argue that the drug has already been approved and determined to be safe by the FDA, so the risk it poses to the public is minor. While off-label prescriptions have been tested for Phase I trials and so are non-toxic if taken under the same conditions and dosages for which they have been approved, there is nothing to indicate that they are safe at different dosages or in combination with other drugs. As we saw in the phen-fen fiasco, drugs that may be safe by themselves can be quite harmful when taken in concert. Phen-fen was only prescribed for a few years and yet it caused heart valve damage in at least 285,000 people.²⁷⁵ Had the drug manufacturer been able to advertise the off-label combination directly to doctors in a widespread promotional campaign the number of people harmed would likely have been considerably higher.

The market plays some role in regulating the behavior of drug manufacturers. Certainly, drug manufacturers certainly do not want the negative publicity and tort liability that comes with marketing a dangerous drug. However, without regulation and oversight from the FDA, we leave it in the discretion of the drug companies to decide how many lives to risk by marketing a potentially unsafe off-label use for a drug. If the consequences of so doing are the damage to reputation and potential litigation liability, then a drug manufacturer will likely operate as do car manufacturers and other less regulated manufacturing industries when calculating these risks. They will determine the potential profits they can get from selling their product which they know to be dangerous and then subtract the potential tort liability and reputational damage. If selling the drug will produce more profits than it will cost, then the manufacturer will likely go ahead and sell it. When a new drug can bring in billions of dollars of revenue, it is likely that manufacturers will choose to gamble with people's lives somewhat frequently. We accept this

²⁷⁵ Wilsker, *supra* note 252, at 840.

reality in the auto industry perhaps because consumers can more easily detect the risks associated with cars. For example we know that a small car is more dangerous than a big one, a car made of steel is safer than one of aluminum, cars with gas tanks in places likely to get hit in an accident are more dangerous with cars with gas tanks in shielded areas. However, a patient cannot look at a pill and determine if it will be safe. We thus need the FDA, which has the resources and expertise required to determine drug safety to oversee the marketing of drugs to doctors and patients.

Moreover, even if an off-label drug does not cause direct harm to a patient, we want our patients to get the most effective treatments. However, if drug companies have no incentive to conduct research on the effectiveness of their drug, or are only motivated to conduct shoddy research that puts their product in the best light, there will be no way for doctors to gather that information. Doctors do have scientific training to be able to see through mere advertising tricks. However, we do not want doctors to have to spend the time to research each drug company's research methods to determine which companies claims are most accurate. And if drug companies are not conducting research on off-label uses or are not compelled to share their data with the public, even well trained doctors will have little else to turn to but the marketing campaigns. Without oversight from the FDA ensuring that drug companies are providing only honest, accurate, and complete information to doctors, it is more likely that doctors' selection of drugs will be based on the effectiveness of the advertising campaign rather than the effectiveness of the drug.

B. INFORMED PATIENT CONSENT

In the midst of the phen-fen controversy in the late 1990s, scholars and the popular media began calling for expanding the informed doctrine to include off-label status.²⁷⁶ The calls for informed consent have died down in the national media. However, scholars and academics still propose informed consent as a cure all for whatever problems they identify with the current off-label marketing regulations.²⁷⁷ The arguments put forth by Steven Salbu and Margaret Johns typify the way scholars on different sides of the debate suggest employing informed consent to improve the off-label marketing regulations.

Johns argues that the current FDA regulations are insufficient to protect patients from aggressive marketing of off-label uses to doctors and potentially insufficient research on the unapproved uses. Johns then proposes supplementing the current FDA regulations by expanding state tort law doctrine of informed consent to require full patient disclosure whenever a doctor prescribes a drug off-label.²⁷⁸ While she admits that this may not reduce the health risks of under researched drugs,²⁷⁹ she argues that current scheme ignores “patient autonomy and self-determination.”²⁸⁰ Because there are inherent risks associated with taking a drug off-label that the FDA cannot make up for through its regulatory scheme, patients should know of these risks when deciding whether to take a drug.²⁸¹ Further, Johns argues that doctors’ decisions about which drugs to prescribe are frequently influenced by pharmaceutical companies. She thus advocates for mandatory disclosure to patients of any “drug company influences that create

²⁷⁶ See Beck & Azari, *supra* note 179, at 71.

²⁷⁷ See, e.g., Johns, *supra* note 193; Salbu, *supra* note 141. See also *id.* (noting how ubiquitous the proposal for informed consent was in the media and academic literature).

²⁷⁸ Johns, *supra* note 193, at 1013.

²⁷⁹ *Id.* at 101.

²⁸⁰ *Id.*

²⁸¹ *Id.*

conflicts of interest or the appearance of conflict of interests.”²⁸² Disclosure of conflicts of interests will make patients more cautious when taking prescribed medications. Patient caution, Johns contends, will counterbalance the excessive influence of pharmaceutical marketing and possibly save lives.²⁸³ Moreover, she argues that disclosure of conflicts of interest will prevent doctors from engaging in “the most egregious” practices, such as prescribing unnecessary drugs or high risk drugs because of a financial relationship with a pharmaceutical company.²⁸⁴

In contrast, Salbu advocates for informed patient consent as part of his proposal for the almost complete deregulation of off-label marketing. Salbu argues that the complex FDA regulations and rules are too broad. He suggests then that we shift some of the burden and responsibility for patient protection from the FDA to patients in the “interests of free speech and medical advancement.”²⁸⁵ According to Salbu, full patient disclosure is the best way to achieve the shift of decision-making to patients.²⁸⁶ When prescribing a drug for an off-label use, doctors should have to disclose that the FDA has not approved the off-label treatment and tell them the potential risks and benefits of taking the drug. “This approach empowers patients and erodes what can be an insultingly paternalistic institution that treats patients more as objects than as active participants in their own treatments.”²⁸⁷

Salbu and Johns are correct that informed consent will give patients more autonomy in that they will have more information with which to decide whether to take a drug. However, the information they have will be almost meaningless because patients lack the scientific and medical background to fully understand the risks they are taking. More importantly, much of the

²⁸² *Id.* at 1019-20.

²⁸³ *Id.* at 1022-23.

²⁸⁴ *Id.*

²⁸⁵ Salbu, *supra* note 141, at 223.

²⁸⁶ *Id.* at 224.

²⁸⁷ *Id.*

information about safety and risks that would be relevant to their decision is unavailable to them and their doctor.

Under an expanded informed consent regime, doctors would have to tell their patients if they prescribe a drug off-label. Without understanding the FDA approval process, simply knowing that a drug is “off-label” gives the patient very little information on which to make a decision about whether or not to take the drug. Under the current informed consent doctrine, doctors are required to tell patients the risks and benefits of treatments they prescribe whether or not the treatment is off-label.²⁸⁸ So, if the doctor is aware of any risks, she will tell her patient whether or not there is an informed consent requirement. And if the doctor does not think the drug particularly risky, without required informed consent she will not say anything to the patient. The only thing that informed consent adds is that, in this case, the doctor must tell the patient that the drug has been approved as safe to take for another use but also works for the one that will help the patient. Likely this information will do little to raise alarm bells in patients’ minds because they will know that the FDA has approved the drug and allowed it onto the market. Thus, the patient is in the same place under an informed consent regime than he was in without one: in the case of a treatment that the doctor views as risky, her doctor must inform her of the risks involved in the treatment. In the case of treatments that her doctor does not view as risky, she must rely on her doctor’s belief that the treatment is safe.

Because informed consent adds little to protect patient’s safety, it is insufficient to compensate for the lack of FDA oversight over off-label marketing as Steven Salbu suggests. Similarly doctors who prescribe drugs because of special relationships with drug manufacturers,

²⁸⁸ Beck & Azari, *supra* note 179, at 100.

are liable in tort and so adding an informed consent requirement that doctors reveal conflicts of interest adds little to patient safety.

Not only may the informed consent requirement be ineffective to protect patient safety, but Beck and Azari also argue that it actually hinders doctors in providing quality medical care. They argue that the FDA status of a drug is irrelevant because it is not “medical information” that can help a patient make an informed decision about treatment options.²⁸⁹ Requiring doctors to inform patients of drugs off-label status would force physicians, who are already struggling to keep up with medical advances that can help their patients, to learn and explain the complex FDA regulatory scheme. Moreover, they argue that this expanded informed consent doctrine would generate a huge number of new claims, “given the ubiquity of off-label use. Nothing would be gained, and much valuable time would be lost, if physicians had to divert their energies from treating their patients and keeping abreast of medical advances to reviewing FDA administrative law.”²⁹⁰ Beck and Azari further contend that patients would be confused and mislead by the information because it might cause them to overestimate the risk associated with taking a drug off-label; it could thus frighten patients from the therapies that would be best for their health.²⁹¹

However, Beck and Azari’s predictions seem a bit overstated. While expanding the informed consent doctrine would likely lead to an increase in tort claims, it is easy enough for doctors to protect themselves by disclosing the off-label status of the drugs. Moreover, doctors likely already understand the FDA drug approval process enough to explain it to their patients without having to read the Federal Register or take “a course in the federal regulation of drugs

²⁸⁹ *Id.*

²⁹⁰ *Id.* at 101.

²⁹¹ *Id.*

and medical devices.”²⁹² It would likely not be as cumbersome a requirement as they suggest. However, even though the harm involved in telling patients that a drug is prescribed off-label may be minimal, so too is the benefit. It will thus not serve to replace the FDA in protecting patients from unsafe drugs nor will it significantly bulwark patient protection as an addition to the current regulatory scheme.

C. CHANGING FDA POLICIES AND PROCEDURES

Rather than focusing on the overarching statutory or regulatory scheme, another group of scholars focus on changing the FDA's processes and procedures to address the problems that they have identified with the off-label marketing scheme. The specific policy and procedure proposals that scholars advocate are diverse. However, these proposals are generally based on one of two presumptions. One group of scholars believes that the government has “tipped the scales towards the end of tightly restricting drug promotion and the drug manufacturer’s freedoms to inform the public about their products.”²⁹³ However, the government’s efforts to protect patient safety have cost patients access to new drugs and innovative treatments. These authors thus propose changes to FDA policies and protocols that will encourage research and make the regulations less cumbersome for drug manufacturers. The other group of scholars argues that the deregulation of off-label marketing places research and economic well being of pharmaceutical companies ahead of patient safety. These scholars then propose changes that augment FDA review of testing and marketing of new uses of approved drugs.

²⁹² Beck & Azari, *supra* note 179, at 101.

²⁹³ Helm, *supra* note 19, at 180-81; *see also* Weeks, *supra* note 66, at 652.

1. Liberalizing Off-Label Marketing Restrictions

Katherine Helm argues that the combination of the cumbersome pre-market approval process for new uses of approved drugs and the introduction of early entry of generic drugs into the pharmaceutical market “stifle the incentives of pharmaceutical companies to obtain further patent protection on and regulatory approval for new uses of approved drugs already on the market.”²⁹⁴ Helm then seeks to speed up the pace at which drugs are approved for new uses and brought to market. Getting drugs approved for new uses sooner will encourage drug manufacturers to conduct rigorous clinical trials about new uses because they will be able to profit from the new uses before generics enter the market. It will also help patients who will have increased access to new treatments earlier.

She thus advocates for reducing the requirements for pre-market approval for new uses for approved drugs supplemented by increased post-market surveillance and “risk assessment of approved drugs, to identify non-evidence-based prescribing practices and to distinguish between those that are clinically reasonable from those that may be of concern.”²⁹⁵ Helm praises the 2007 FDA Amendments for focusing on increased post-market surveillance of drugs.²⁹⁶

Increased post-market surveillance of drugs will help to identify potential off-label uses and detect safety hazards that were not revealed during the pre-market clinical trial period. However, post-market surveillance cannot prevent unsafe drugs or drug combinations from getting to the market in the first place. Moreover, even with post-market review, it will likely take a significant amount of time for the research to detect adverse effects. In the time it takes to detect this danger and remove the drug from the market, hundreds of thousands of patients could

²⁹⁴ Helm, *supra* note 19, at 185.

²⁹⁵ *Id.* at 182-86.

²⁹⁶ *Id.* at 184.

be harmed or even killed. For example, phen-fen was popular only between 1992 and 1997.²⁹⁷ In that time at least 285,000 people had heart valve damage from taking the drug combination.²⁹⁸ Post-market surveillance may catch adverse effects more quickly than they were discovered in the phen-fen situation. However, under Helm's regime, the drug manufacturer would be marketing the drug to a widespread audience while the data was being generated, meaning the number of patients taking it in the meantime might dwarf even the numbers who were taking phen-fen. Moreover, even if the drug is not unsafe, it may be ineffective and we do not want large numbers of people taking an ineffective drug and losing valuable treatment time, while we wait to find out if it is really effective.

Thus, while Helm's suggestion of post-market research is a good idea to supplement the knowledge we have about drugs that are already approved, it will not protect patients from unsafe or ineffective drugs that get onto the market place. We may be willing to accept this risk for patients on a small scale so that we can get effective treatments to them. However, should we allow widespread marketing of drugs conditional mostly on post-market research, a huge number of patients could be injured while we wait to find out if the drug is actually safe. In the case of drugs for life threatening or severely debilitating diseases, such as HIV and AIDS, Helm's proposal for an abbreviated pre-market approval process supplemented by post-market surveillance makes sense because the potential risks of the drug are likely less than the patients' certain outcomes without it. However, the FDA already employs such a system.²⁹⁹ For drugs where the benefits are not that significant, the risk then seems too high.

²⁹⁷ Wilsker, *supra* note 252, at 841.

²⁹⁸ *Id.*

²⁹⁹ HUTT & MERRILL, *supra* note 11, at 559.

Elizabeth Weeks argues that the liberalized dissemination provisions of the FDAMA intended to get reliable information about innovated treatments into the hands of doctors.³⁰⁰ However, the cumbersome and time consuming approval process for supplemental new drug applications keeps drug manufacturers from taking advantage of the provisions. Weeks suggests that the FDA prioritize approval of supplemental applications that are submitted by manufacturers seeking permission to promote drugs for unapproved uses. FDA approval is advantageous to manufacturers because it increases a drug's marketability and increases sales. She argues that priority review will "protect FDA's mandate to ensure that accurate and thorough research is conducted regarding the safety and efficacy of new uses, while still providing an incentive to manufacturers in the form of expedited approval."³⁰¹ Thus, through priority review, the FDA will be able to achieve the dual aims of protecting patients from unsafe or ineffective drugs while at the same time promoting innovation and getting new treatments to market faster.³⁰²

Of course it is a good idea to expedite getting new treatments to market. Unfortunately, the FDA is an agency of limited resources. Without an additional funding, if the FDA prioritizes all supplemental drug applications, it must either demote the priority of other applications or slow down the approval process for all non-priority applications even more. Weeks' proposal then will not ensure that more new treatments get to the patients who need them more quickly. Rather, she is simply trading which class of drugs gets into the hands of patients sooner. Certainly, expedited review of supplemental drug applications for companies wishing to market drugs for off-label uses will get these drugs to patients sooner. However, the cost of so doing

³⁰⁰ Weeks, *supra* note 66, at 664.

³⁰¹ *Id.*

³⁰² *Id.*

will be that other drugs, perhaps new drugs or generics will get to market and to the patients who need them more slowly. Weeks' proposal then simply trades one problem for another.

2. Strengthening Off-Label Restrictions

Michael Oates argues that because manufacturers do not have to demonstrate efficacy for unapproved uses, research about novel uses is deficient.³⁰³ He argues that under the current regulations, manufacturers have few incentives to undertake clinical trials to test the safety and efficacy of new uses for approved drugs that are already on the market.³⁰⁴ And, even when manufacturers conduct trials, the trials do little to help the public because they are under no duty to disseminate the results.³⁰⁵ Oates argues that market forces will likely be insufficient to motivate drug manufacturers to conduct the research necessary to test new uses of drugs.

Therefore, he proposes a regulatory and legislative scheme modeled after the Best Pharmaceuticals for Children Act (BPCA) in which the government mandates post-approval trials for off-label uses of some drugs. In the BPCA, the government identifies potential off-label uses of drugs and then provides funding for clinical trials to test those uses for children when the manufacturer refuses to do so.³⁰⁶ In Oates' plan, post-approval research would be required for all drugs that are regularly prescribed off-label. The government would assist with funding for the clinical trials on a sliding scale based on the profits the company makes from the off-label use.³⁰⁷ Oates also suggest that the FDA should participate in the analysis of the data to

³⁰³ Oates, *supra* note 141, at 1272.

³⁰⁴ *Id.* at 1283-86.

³⁰⁵ *Id.* at 1286-89.

³⁰⁶ *Id.* at 1304.

³⁰⁷ *Id.* at 1306-07.

make sure that the results are sound and the results of these studies must be made publicly available.³⁰⁸

Jaime Wilsker is also concerned with the lack of incentives for manufacturers to conduct post-approval research for unapproved uses of drugs. In his Note, *One-Half Phen in the Morning/One Fen Before Dinner*, Wilsker contends that drugs dispensed in combination with each other should be treated like a new drug and should have to go through the FDA's NDA process.³⁰⁹ He cites the phen-fen experience, in which at least 285,000 patients suffered heart valve damages, during the short period when the two drug combination was widely prescribed for weight loss,³¹⁰ to argue that two drugs, which used alone are harmless, may be deadly when prescribed in combination.³¹¹ Because the FDA testing on safety will not reflect this danger, Wilsker argues that public safety requires the FDA to review new combinations of drugs the same way they would review new drugs that have yet to enter the market.³¹²

Oates and Wilsker's proposals would increase patient safety, but they would do so at the expense of getting new therapies into the hands of the patients who need them. Both of these plans require substantial resources. Unless Congress was to appropriate additional funds for these endeavors, they would require that the FDA divert financial and other resources from other initiatives to fund these initiatives. Thus, while these both may be good ideas, they, like Week's proposal, merely promote one value over another. For example, Wilsker is correct that drugs prescribed in combination may present new dangers that the drugs alone would not. He is also correct that the FDA's current regulatory scheme allows this danger to persist. However, his

³⁰⁸ *Id.*

³⁰⁹ Wilsker, *supra* note 252, at 844-47.

³¹⁰ *FDA Announces the Withdrawal of Fenfluramine and Dexfenfluramine*, HHS NEWS, Sept. 15, 1997, at 97-32; Salbu, *supra* note 141, at 203.

³¹¹ Wilsker, *supra* note 252, at 827-37.

³¹² *Id.* at 844-49. *See also* Salbu, *supra* note 141, at 205 (discussing Wilsker's conclusion).

suggestion that the FDA must review all drugs prescribed in concert as new drugs would likely cause significant delays in getting useful drugs to market and might cost as many lives for lack of treatment as it saves. For example, many of the treatments for HIV and AIDS are cocktails of several drugs prescribed together. Under Wilsker's plan, these drugs would have to be approved as new drugs before being prescribed in concert. In the time it takes drug makers to put together clinical trials and the FDA to review them, even under expedited review, thousands of patients could die or have their disease progress far more rapidly than it would have had they had access to the medications.

Likewise, Oates' plan requires providing drug manufacturers with supplementary funding to conduct post-approval research on new uses for drugs. And it mandates that the FDA be involved in analyzing the data collected in these trials. However, these innovations come at a cost. FDA scientists who are currently involved in designing and overseeing clinical trials, will now be responsible for also overseeing these clinical trials as well. Without significant new resources, this will simply slow down the approval of study design for new drugs and delay getting new drugs to market.

VI. A NEW PROPOSAL TO PROMOTE EDUCATION OVER PROMOTION

There are shortcomings to the off-label marketing scheme originally created under the FDAMA and most recently suggested in the Draft Guidance: it allows manufacturers to disseminate information about off-label uses that endanger patients; it stifles innovation somewhat since manufacturers are not able to profit fully from new innovations; and it limits the number of patients who will be aware of and have access to treatments that could potentially benefit them. However, these shortcomings all reflect the fact that the FDA is charged with the

promoting the competing interests of trying to get safe, effective, and reliable treatments to patients and doctors as quickly as possible and protecting the public from unsafe and ineffective drugs. To this end the FDA has sought to strike a balance between promoting education of doctors and the dissemination of reliable information about new uses to patients while still protecting the public from widespread harm and trying to encourage drug manufacturers to submit NDAs.

What all of these proposals have in common is that they seek to recalibrate the balance either towards increased protection from harmful drugs or faster distribution of potential new treatments. However, the above examination of each of the proposals demonstrates that, like with any system trying to balance competing interests, strengthening one interest necessarily weakens the other. Thus, all of these proposals seeking to change the over-arching regulatory balance attempt to plug one leak by removing the stopper from another. One plan may help more patients to get more treatments but it will do so by allowing more patients to take dangerous drugs. And another plan may prevent more patients from taking dangerous drugs, but it will do so by allowing those in need of treatments to suffer.

With all of its present shortcomings, the current FDA scheme suggested under the Guidelines seems to best balance the competing interests between innovation and access to new treatments with protecting patients from under researched drugs. It prohibits the widespread marketing of drugs that have not been tested for efficacy and safety while at the same time allowing manufacturers who are willing to undertake the clinical trials necessary to demonstrate safety and effectiveness to disseminate reliable research findings to doctors. It thus emphasizes education rather than promotion.

This distinction between education and promotion is an important one. Promotion seeks to sell a product, it thus inherently wants to emphasize the benefits of the product while at least underemphasizing the risks. Education on the other hand has no motive other than to disseminate unbiased information to those who need it. We should be focused on promoting education rather than promotion. However, most of the proposals for change put forth in the academic literature ignore this distinction between education and promotion. The academic literature seems to take as a given that drug manufacturer promotion is the only way to get information out to doctors and patients; thus, they simply accept that biased information is the only type of information that we can provide to doctors. In proposing solutions then, academics focus on either reducing the review standards and regulations, which they see as barriers to promotion, or increasing these barriers for promotion.

However, if the goal is to get patients and doctors reliable information about safe new treatments while still protecting them from experimental or under-researched drugs, the focus should be on promoting education while still restricting promotion. This emphasizes making sure that the information that doctors receive is scientifically sound and unbiased. By permitting drug companies to disseminate only full reprints of articles published in peer-reviewed reputable scientific and medical journals, the FDA regulations help to ensure that the information doctors receive about off-label uses is unbiased. Moreover, by reviewing the materials before they go to doctors, the FDA can make sure that the studies and the results that they are publishing are scientifically sound. In these ways, the FDA is on the right track towards promoting doctor education.

However, the current regulations and guidelines significantly limit the number of doctors who get this information. First, drug manufacturers must mail full articles to doctors who may or

may not have time to read them. Second and more importantly, a doctor must receive the article from the drug manufacturer or hear of it from one of his peers in order to know it exists.

According to the American Medical Association, there are nearly a million licensed doctors practicing in the United States today.³¹³ It would be incredibly expensive for pharmaceutical companies to determine which of the million practicing physicians treat patients with the conditions that their product treats. Moreover, even if pharmaceutical companies could effectively target these doctors, for example finding a list of current oncologists in the United States, for pragmatic and economic reasons, drug companies can likely only reach a handful of these doctors through direct mailing of journal articles. Thus, huge numbers of doctors are left without the most cutting edge information to treat their patients. Because of these limitations, pharmaceutical companies failed to disseminate information under Section 401 of the FDAMA. The Draft Guidelines does nothing to solve these problems.

What we should be looking for then, are ways to get the FDA vetted information into the hands of doctors who need it. A searchable database maintained by the FDA offers one means of doing this. If a drug manufacturer submitted materials to the FDA that it wants to disseminate, the agency could enter the drug name, off-label indication, and cites to the articles and research supporting the indication into a database.³¹⁴ Then, doctors looking for a treatment for their patients could simply login to the database and search for drugs that may be beneficial for their patients.

³¹³ American Medical Association, Access Physician Statistics Now: Physicians in the United States and Possessions by Selected Characteristics, <http://www.ama-assn.org/ama1/pub/upload/images/373/internettable.gif> (last visited May 9, 2008).

³¹⁴ Admittedly, under the Draft Guidelines, manufacturers are not required to submit their materials to the FDA prior to dissemination. However, access to publication in a database such as this one would likely motivate manufacturers to do so.

Unlike some of the above-suggested solutions, this database would not be significantly costly to maintain. Under the FDAMA, the FDA reviewed and approved the materials that drug manufacturers wish to disseminate to doctors for off-label uses. It also maintained records about what materials the drug companies are sending to which doctors. So this system would add few additional costs as compared to the FDAMA. This solution would also likely motivate pharmaceutical companies with drugs that have promising new indications to submit supplemental NDAs because it would enable the type of targeted and effective marketing that could significantly impact sales. In this case, rather than having to pay for blanket mailings to many doctors who will likely never read them, pharmaceutical companies would be able to reach all of the doctors who are looking for treatments that their drug targets. In this way, this “marketing” would be more effective than even widespread promotion because pharmaceutical companies would be able to reach people who were serious about purchasing their product.

Moreover, this solution would help to weed out those products that may be less effective or dangerous. Because drug companies that send out materials under the dissemination provisions can only reach a limited number of doctors, they can only marginally increase sales over simply publishing a study in a medical journal. It is therefore likely that even drug companies with promising drugs do not submit the NDA to enable them to take advantage of the off-label dissemination provisions of the FDAMA. However, since this database would reduce the cost of disseminating information for manufacturers while greatly increasing their access to doctors and patients looking for their treatment, it is likely that many more drug companies would want to take part. Doctors might then presume that if a drug is not listed in the database it is because the drug manufacturer could not get a study published in a reputable

journal or did not want to submit to FDA review for some reason. This would motivate drug companies with promising new uses to submit the SNDA to avoid this presumption.³¹⁵

This database is only one way to promote doctor education within the current regulatory scheme while still protecting patients as well. Another example is that drug manufacturers who are eligible to distribute materials on off-label materials to doctors could have up to two or three-off-label indications listed in the Physicians Desk Reference while they await their supplemental new drug approval. Indeed this plan is not perfect. By increasing the number of doctors who are aware of these off-label indications, we increase the risk of patient harm. However, that occurs in any case where there is an increase in the number of patients taking any pharmaceutical product. Moreover, by helping pharmaceutical companies reach doctors who are looking for their product, this system offers incentives for pharmaceutical companies to abide by FDA regulations, rather than attempt to circumvent it.

CONCLUSION

Since it began regulating human drugs, the FDA has tried to balance the interests of patient safety with making new therapies and medications accessible to patients as quickly as possible. Responding to tragedies such as the Elixir Sulfanilamide fiasco, which killed over 100 people in the 1930s, during the better part of the twentieth Century, the FDA tightened its regulations to increase patient safety. And for several decades in the latter of half of the

³¹⁵ Manufacturers that produce drugs targeting exotic diseases with very small patient populations may not submit a SNDA because the number of patients it could reach even through the database would not be cost effective. However, in this case, doctors treating these conditions would not be worse off because they would still have the other available channels for receiving information that they have currently. Moreover, the drug manufacturers would not be impacted by this presumption because doctors would realize that they are dealing with an exotic condition, which is likely not listed in the database. However, if a manufacturer with a new treatment for lung cancer chose not to list it in the database, it could be a red flag to a doctor that the treatment may not be as effective or promising as previously thought.

twentieth century, the FDA maintained a complete prohibition of all off-label marketing of approved drugs. However, as the rate of medical innovation sped up and the AIDS crisis created a need for rapid access to new therapies, the FDA has begun to shift the regulatory balance back in the other direction towards promoting research and drug access to patients in recent years. This was the purpose of the FDAMA's new policy allowing for the limited dissemination of information of off-label drug indications, which sought to increase patient access to innovative uses of approved drugs while still protecting the public from exposure to novel and dangerous therapies.

But, this policy and the regulations that the FDA promulgated under it drew significant criticism. One group of critics argue that the policy does not do enough to promote research and keeps patients who need them from getting access to safe drugs. The other group of critics argues that any promotion of off-label uses of drugs endangers the public by exposing them to under-researched drugs and treatments and reduces the incentives for drug companies to submit new uses to the FDA for approval. Ultimately, because it was so burdensome and did not substantially increase drug manufacturer's access to patients, few pharmaceutical companies took advantage of the provisions and they expired in 2006.

Critics on both sides of the debate were correct. The regulatory balance under the FDAMA restricted some patients from access to innovative treatments that could help them and endangered others by exposing them to drugs that have not been fully tested. However, it was likely the best balance that the government can reach, which is reflected by the fact that the FDA's Draft Guidelines seek to establish an almost identical system. Moreover, by focusing on promotion by drug manufacturers rather than education, this debate is looking at the wrong

issues; rather than fighting about which interest is more important, safety or innovation, we should be trying to find a way to promote both interests at the same time.

Off-label treatments are some of the most cutting edge in medicine today and are the primary methods of treatments for diseases such as HIV and AIDS and cancer. As long as we have a system where off-label prescribing remains as prevalent as it is today, we must find a way to get doctors the most accurate and unbiased information we can. A database that provides physicians with unbiased scientific information about new indications for already approved drugs would provide doctors with invaluable information. Moreover, being able to reach doctors looking for innovative treatments through such a database would cut the cost of information dissemination for pharmaceutical companies while increasing their incentives to submit SNDAs. By looking for solutions such as this which focus on fostering physician education rather than loosening restrictions on drug promotion manufacturers, the FDA can further the dual ends of promoting research and innovation while still protecting patients from under-researched and dangerous drugs.